Minimal phenotyping yields genome-wide association signals of low specificity for major depression

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Other studies referenced in this paper

We have summarised the other studies we reference in our paper, summary statistics of many of which are available on the Psychiatric Genomics Consortium website, in Supplementary Table 1. For each of the studies, we use only those SNPs with imputation INFO score above 0.9 and MAF > 5% in estimation of heritability, partitioned heritability, and genetic correlation.

Imputed genotype quality control

We performed stringent filtering on imputed variants (version 2) used for GWAS in this study, removing variants not among the 33,619,058 variant sites in the Haplotype Reference Consortium[75] (HRC) panel, then removing all insertions and deletions (INDELs) and multi-allelic SNPs. We hard-called genotypes from imputed dosages at 8,968,715 biallelic SNPs with imputation INFO score greater than $0·9$, MAF greater than $0·1\%$, and P value for violation of Hardy-Weinberg equilibrium $> 10^{-6}$, with a genotype probability threshold of $0·9$ (anything below would be considered missing). Of these, 5,276,842 SNPs are common (MAF > 5%). We consistently use these SNPs for all analyses in this study.

Sample filtering

Of all 502,637 samples in UKBiobank full release, we performed the following QC steps to select the samples for use in our analyses. We first removed samples that were not included in the UKBiobank full release PCA analysis, which includes samples that were indicated as "het.missing.outliers" ("Indicates samples identified as outliers in heterozygosity and missing rates, which indicates poor-quality genotypes for these samples"), "excess.relatives" ("Indicates samples which have more than 10 putative third-degree relatives in the kinship table"), and whose "Submitted.Gender" were different from "Inferred.Gender". Applying these filters brought the sample size down to 407,219. We checked that the remaining sample contains only one out of any pair or group of related individuals with relatedness > 0.05.

We then selected samples indicated to be "in.white.British.ancestry.subset" ("Indicates samples who self-reported 'White British' and have very similar genetic ancestry based on a principal components analysis of the genotypes"), resulting in a sample size of 337,545. We then removed 337 samples indicated as having "putative.sex.chromosome.aneuploidy" ("Indicates samples identified as putatively carrying sex chromosome configurations that are not either XX or XY"). Finally, we removed 7 samples who have withdrawn their consent for use of their genetic data in analyses, arriving at our final set of 337,198 samples passing QC[1].

Of these samples, 37,041 were part of UK Biobank Lung Exome Variant Evaluation (UKBiLEVE), a study for chronic obstructive pulmonary disease (COPD). We retain all samples in UKBiLEVE, but as they are genotyped using a custom array optimized for coverage over regions implicated in lung health and disease[2], we consistently use genotyping array as a covariate in all our analyses.

For our analyses on different definitions of depression in UKBiobank, we further excluded 2,499 samples that indicated as having a history of substance abuse ("alcohol dependency": 1408, "opioid dependency": 1409 or "other substance abuse/dependency": 1410), manic or psychotic conditions (in the "Non-cancer illness code, self-reported" (data field 20002) section of the verbal interview, or who are classified under "Bipolar I Disorder" or "Bipolar II Disorder" in the "Bipolar and major depression status" (data field 20126) derived data field, giving a total of 334,699 samples for our study of the different definitions of MDD in UKBiobank.

Minimal phenotyping definitions of depression in UKBiobank

There is evidence that self-reported diagnoses often over-estimate the prevalence of MDD based on interviews (for example in one population survey self-report questionnaire gave an estimate of 22.6%,

compared to 8% based on interviews[59]). Agreements between self-report measures and clinician ratings are low[60], as are test-retest reliabilities from clinicians in general practice (kappa coefficients of around 0.3 in DSM-5 field trials[61]. This is in contrast to high inter-rater reliability between trained clinicians following diagnostic manuals (kappa coefficients of around 0.7 in both DSM-3[62] and DSM-4[63] field trials).

We define three minimal phenotyping-based definitions of depression in UKBiobank, each based on one or two questions instead of the full DSM-V diagnostic criteria, all of which are shown in Figure 1.

First, we identified 115,360 individuals who had sought help for "nerves, anxiety, tension or depression" from either their general practitioner (GPpsy, 113,260 out of 332,633, data field 2090) or a psychiatrist (Psypsy, 36,286 out of 333,412, data field 2100). 34,186 (29.6%) of those who sought help have seen both a GP and a psychiatrist. These make up most of the cases if the "broad depression" phenotype in Howard et al 2018[3], which we refer to and discuss in detail in the Supplementary Methods section "Comparison of definitions of depression in UKBiobank with those from previous GWAS".

Second, participants from 10 out of 21 assessment centers were asked whether they had ever experienced apathy and/or low mood (data fields 4631 and 4598), and how long they experienced it for (data fields 5375 and 4609). Having one or more of the two symptoms for 2 weeks or more is necessary, but not sufficient, for a DSM-V diagnosis of MDD. We applied this criterion together with help-seeking on the cases in GPpsy and Psypsy to identify 21,177 symptomatically defined cases (DepAll, data field 20126, returned by Smith et al 2013[4] which applied the same criteria), making up 70.7% of GPpsy and 78.0% of Psypsy who answered the questions on the two cardinal symptoms. Smith et al 2013[4] further divide these individuals into the following sub-categories: those with a single episode (DepSingle, 5,440 cases), and those with recurrent episodes of moderate depression (so defined because they were only examined by their primary care physician - DepRecurMod, 10,142) or severe depression (so defined because they were examined by psychiatrists - DepRecurSev, 5,595 cases). In this study, we do not consider the distinctions between these sub-categories.

Third, we identified 19,805 cases who self-reported having depression (SelfRepDep) during a verbal interview with a trained nurse (data field 20002, code 1286).

Electronic health record-based definition of depression in UKBiobank

We derive an electronic health record (EMR)-based definition of depression using the ICD10 codes in UKBiobank for both primary (data field 41202) and secondary diagnoses (data field 41204).

To qualify as a case of EMR-based definition of depression in UKBiobank, we require individuals to have a ICD10 code for any of the mood or affective disorders for either a primary or a secondary diagnosis, including: depressive episodes (F32), recurrent depressive disorder (F33), persistent mood (affective) disorders (F34), other mood (affective) disorders (F38), or unspecific mood (affective) disorders (F39). This is consistent with the definition of "ICD10-coded depression" in Howard et al 2018. Controls are those individuals who have not had either a primary or a secondary diagnosis of any of the above.

We then exclude from both cases and controls in this definition individuals that have the following primary or secondary diagnosis: delirium, not induced by alcohol and other psychoactive substances (F05), other mental disorders due to brain damage and dysfunction and to physical disease (F06), personality and behavioural disorders due to brain disease, damage and dysfunction (F07), unspecified organic or symptomatic mental disorder (F09), mental and behavioural disorders due to psychoactive substance use (F10-F19), schizophrenia, schizotypal and delusional disorders (F20-29), manic episodes (F30), and bipolar affective disorder (F31). Some of these other conditions are also excluded in "ICD10-coded depression" in Howard et al 2018, as we detail in the Supplementary Methods section "Comparison of definitions of depression in UKBiobank with those from previous GWAS".

Strictly defined, CIDI-based definition of MDD in UKBiobank

We derive a CIDI-based based *in silico* diagnosis of lifetime MDD using the CIDI questionnaire from the online mental health follow-up assaying DSM-V[5] symptom criteria for MDD (data category 138).

To qualify as a case of lifetime MDD according to DSM-V criteria, we first require individuals participating in UKBiobank to answer "Yes" to either the questions "Have you ever had a time in your life when you felt sad, blue, or depressed for two weeks or more in a row?" (data field 20446, DSM criterion A1 in Supplementary Table 2) or "Have you ever had a time in your life lasting two weeks or more when you lost interest in most things like hobbies, work, or activities that usually give you pleasure?" (data field 20441, DSM criterion A2 in Supplementary Table 2). Both are cardinal symptoms for DSM-V defined MDD. We then require them to have 3 or 4 among the criteria A3-A9 shown in Supplementary Table 2. We note that this questionnaire does not contain the DSM criterion A5, which requires "Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)", and hence assays only 8 out of the 9 symptoms for DSM-V MDD. Nonetheless, we require individuals to have a total of at least 5 symptoms, including at least one out of the two cardinal symptoms (A1 and A2) such that they have at least 5 out of 9 symptoms for DSM-V defined MDD, to fulfil the DSM-V A criterion: *Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure*.

To qualify as a case of current MDD according to DSM-V criteria, we first require individuals participating in UKBiobank to answer "Nearly every day" to cardinal symptoms "Feeling down, depressed, or hopeless" (data field 20510, DSM criterion A1 in Supplementary Table 2)" or "Little interest or pleasure in doing things" (data field 20514, DSM criterion A2 in Supplementary Table 2)", for the question "Over the last 2 weeks, how often have you been bothered by any of the following problems?". We then require them to have 3 or 4 among the criteria A3-A9 shown in Supplementary Table 2. This questionnaire, unlike the one for lifetime MDD, does contain the DSM criterion A5, which requires "Moving or speaking so slowly that other people could have noticed? Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual", and hence assays all 9 symptoms for DSM-V MDD. We require individuals to have a total of at least 5 symptoms, including at least one out of the two cardinal symptoms (A1 and A2) such that they have at least 5 out of 9 symptoms for DSM-V defined MDD, to fulfil the DSM-V A criterion as described above.

Finally, we require those who fulfil the symptomatic criteria for both lifetime and current MDD to answer "Yes" to the question "Think about your roles at the time of this episode, including study / employment, childcare and housework, leisure pursuits. How much did these problems interfere with your life or activities?" (data field 20440), to fulfil the DSM-V B criterion: *The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning*. Those who fulfil both DSM-V A and B criteria for either lifetime or current MDD are considered a "case" in our CIDI-based definition of MDD, LifetimeMDD. Supplementary Figure 1 shows the percentage endorsement of each symptom, as well as the total number of symptoms endorsed by cases of LifetimeMDD.

We excluded individuals who report a history of substance abuse, as well as manic or psychotic conditions so that our MDD cases all further fulfil criteria C, D and E of DSM-V:

C. The (MDD) episode is not attributable to the physiological effects of a substance or to another medical condition.

D. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.

E. There has never been a manic episode or a hypomanic episode" respectively.

Further, using the question on lifetime number of depressed episodes in the online mental health follow-up (data field 20442), we designated those cases of LIfetimeMDD who indicated they had two or more episodes as cases

for recurrent CIDI-based MDD (MDDRecur) and those who didn't as controls. We show the overlaps between definitions of MDD in UKBiobank in Supplementary Figure 2.

The non-MDD definition of depression

In order to understand the difference between the help-seeking definition of depression GPpsy and the cardinal symptoms-based definition of depression DepAll, we derived another phenotype GPNoDep, which contained individuals who were cases in GPpsy but not DepAll.

DepAll is defined based by answering a) "Yes" to "Ever unenthusiastic/disinterested for a whole week" (data field 4631) with "Longest period of unenthusiasm / disinterest" being greater than or equal to 2 weeks, or "Ever depressed for a whole week" (data field 4598) with "Longest period of depression" (data field 4609) being greater than or equals to 2 weeks, and b) having answered "Yes" to "Seen doctor (GP) for nerves, anxiety, tension or depression" (data field 2090) or "Seen a psychiatrist for nerves, anxiety, tension or depression". These questions are answered by roughly half the participants in the UKBiobank (10 out of 22 collection centres, shown in Supplementary Table 4).

Controls in DepAll are those who have a) answered "No" to either symptoms, b) answered 0 or 1 week for durations of either symptoms, or c) answered "No" to seeing either a GP or Psychiatrist.

Cases in GPNoDep consist of those cases of GPpsy who are controls in DepAll, are those with a) or b). As such, they actively reported that they do *not* have one or other of the two cardinal symptoms of MDD (low mood or lack of interest). This forms 30% of cases in GPpsy who answered questions on the cardinal symptoms and their duration. As those questions on the cardinal symptoms and their duration are asked in individuals in 10 out of 22 collection centres, rather than those selected based on depression related traits, we can assume that collection of the same information in the other 12 collection centres will yield similar results. As such, we assume that those fulfilling case criteira of GPNoDep should constitute around 30% of the cases in GPpsy in UKBiobank.

We were only able to derive GPNoDep because data on cardinal symptoms of MDD was collected using the touchscreen questionnaire at baseline interview in UKBiobank, at the same time as information on whether one has sought medical help for depression was obtained. As such, GPNoDep is not meant to be a "gold standard" non-MDD phenotype, but one that is enabled by collection of information on both symptoms and self-reported seeking of medical attention at the same time point. It is likely that a proportion of cases in GPNoDep may meet criteria for lifetime MDD.

To further validate if cases in GPNoDep have MDD, we examined data collected at a different time point from the touchscreen interview at baseline, through verbal interviews (from which we derived SelfRepDep) or online mental health questionnaire (from which we derived LifetimeMDD).

Of the 58,125 individuals who had answered the questions necessary to have non-missing entries for GPNoDep, 43,613 (75.0%) answered the questions necessary to have a non-missing entry for self-reported depression SelfRepDep through verbal interview. Among this, 7139 are cases in GPNoDep, of which 610 (8.5%) are cases in SelfRepDep. If we take these data at face value, only 8.5% of the cases of GPNoDep who have gone to the GP for medical attention self-identify as having "depression" – a small proportion. Of the same 58,125 individuals in GPNoDep, 15,055 (25.9%) answered the questions in MHQ necessary to have a non-missing entry for self-reported DSM symptoms based LifetimeMDD. Among the 1,541 cases of GPNoDep that answered the MHQ, 307 (19.9%) are cases in LifetimeMDD. Again, if we take these data at face value, about a fifth of the cases in GPNoDep who answered the MHQ self-identify with symptoms that would constitute CIDI-based MDD. Both these findings are only enabled by the availability of self-report of depression or the symptom endorsement data from the online mental health questionnaire (MHQ).

Notably, the proportion of GPNoDep cases who answered the self-reported non-cancer illnesses during the verbal interview (16.4%) is significantly different from the proportion who did not answer (10.0%, Chisq test P $< 10^{-16}$, df = 1). Similarly, the proportion of GPNoDep cases who answered the MHQ (10.2%) is significantly different from the proportion who did not (16.5%, Chisq test P $< 10^{-16}$, df = 1). These numbers are shown in Supplementary Table 3. This shows that the percentages of GPNoDep cases who may qualify for SelfRepDep (8.5%) or LifetimeMDD (19.9%) are likely not an accurate estimate of the proportion of cases in GPNoDep that would self-report depression or qualify for CIDI-based MDD if all of them answered the relevant questions. We have little information to infer further due to the lack of self-report or symptom data on the rest of the cases and controls in GPNoDep. This points to the value of obtaining information on MDD symptoms in data collection.

Features of definitions of depression in UKBiobank for consideration in GWAS

There are several features to these definitions of MDD we recognize as important for the comparison of their genetic architecture. First, for each diagnostic category we used controls who were asked the relevant questions but failed to meet criteria. As such, cases from one category can be controls in another, resulting in substantial overlap in both cases and controls between categories (Supplementary Figure 2), which impacts assessment of genetic architecture and genetic correlation between them[23]. Second, not all participants in UKBiobank were asked questions from all categories. For example, questions for the Symptom-based definition DepAll were asked in only 10 out of 22 assessment centers in UKBiobank (Supplementary Table 4), and the MHQ was only answered in full by 31% of the original UK Biobank participants, resulting in differences in population structure between definitions that need to be considered in analysis (Supplementary Methods, Supplementary Figure 3).

Third, different definitions of depression have different prevalence in the UKBiobank cohort (from 0.078 to 0.341, Supplementary Table 5). Though unlikely biased due to population structure (Supplementary Tables 6-7), the wide range of prevalence may be due to self-ascertainment biases. In general, the UKBiobank is known for higher participation rates from women who are older, more well-off, and better educated[24]. One example of self-ascertainment of particular interest to our analysis is the voluntary participation in the MHQ, which has been shown to have a genetic component that can be genetically correlated with that of mental health conditions[25]. All such biases can have confounding effects on genetic studies of depression phenotypes derived from it. We verified that, though ascertainment biases exist, they cannot account for the results we present in this paper (Supplementary Methods, Supplementary Figure 4, Supplementary Table 8-9).

Finally, many previous GWAS on depression (and any other disease) apply other filters in the selection of cases and controls, in addition to case criteria. One such example is the use of "clean controls" which requires individuals who are designated as "controls" do not endorse any of the case criteria. We do not use "clean controls" in this study, as that violates key assumptions in our analyses of genetic architecture (Supplementary Methods), although we show this strategy can increase power in GWAS as compared to using all controls (Supplementary Tables 10-11, Supplementary Figure 5).

Comparison of definitions of depression in UKBiobank with those from previous GWAS

In this section, we draw direct comparisons between definitions of depression included in this paper with that from previous studies that included UKBiobank data. We found that the minimal phenotyping definitions used in previous cohorts (such as "broad depression" in Howard et al 2018 and 23andMe in Hyde et al 2016, which contribute greatly to the sample size in Wray et al 2018) gave similar findings to help-seeking definitions of depression GPpsy in UKBiobank, while DSM-based cohorts like CONVERGE and PGC1-MDD show similar findings as CIDI-based LifetimeMDD in UKBiobank (see Supplementary Figure 6, cohorts are summarised in Supplementary Table 1). We explore the extent to which this finding reflects the use of the same definitions of MDD.

Cases in Wray et al 2018 are from a meta-analysis of multiple cohorts, including the first release data from UKBiobank. These cohorts are collected with vastly different approaches, and as such it is difficult to draw direct comparisons between the whole meta-analysis and definitions of depression included in this study. We consider individual cohorts from the PGC2-MDD included in Wray et al 2018 in our Supplementary Methods section "Cohorts in the MDD Working Group of the Psychiatric Genomics Consortium (PGC2-MDD)" and our Results section "Out-of-sample prediction of MDD".

Howard et al 2018 used only individuals from the UKBiobank and described in detail how each of the three definitions of depression that were included in their paper were derived, as reiterated below:

1. Broad depression, for which "Case and control status was determined by the touchscreen response to either of two questions: … UK Biobank field: 2090… or …UK Biobank field 2010. Caseness for broad depression was determined by answering "Yes" to either question at either the initial assessment visit, at any repeat assessment visit, or if there was a primary or secondary diagnosis of a depressive mood disorder from linked hospital admission records… The remaining respondents were classed as controls if they provided "No" responses to both questions during all assessments that they participated in."

In this phenotype, cases are the union of our definitions GPpsy, Psypsy, and ICD10Dep. Controls are all those who do not meet criteria for any of these definitions. There is no additional filter of either cases or controls.

2. ICD10-coded depression, for which "Participants were classified as cases if they had either an ICD-9/10 primary or secondary diagnosis for a depressive unipolar mood disorder … controls were participants who had linked hospital records, but who did not have any diagnosis of a mood disorder and were not probable MDD cases".

There is no mention of which ICD9 code was used to derive the ICD9 based cases or controls, so it is assumed that only the ICD10 codes were used in derivation of this phenotype. One additional filter was applied: controls for this definition that are cases for "probable depression" (as defined below) were removed.

3. Probable depression, for which cases and controls were defined "following the definitions from Smith et al… Cases for the probable MDD definition were supplemented by diagnoses of depressive mood disorder from linked hospital admission records (UK Biobank fields: 41202 and 41204) as per the broad depression phenotype."

This phenotype is the same as our definition DepAll, which is also derived from definitions from Smith et al 2013[4], with the addition of cases from ICD10Dep.

As such, all three definitions are combinations of definitions used in our study, but came with more inclusions and exclusions than we used. Here, we explain how these additional inclusions and exclusions are likely to impact their genetic architectures, in comparison to definitions we present in this paper.

First, Howard et al 2018 used information collected at two different time points (Touchscreen questionnaire and electronic medical record) for defining each of their depression phenotypes. Instead of assessing inter-rater liability between the two diagnoses and taking the intersection of cases obtained through two diagnoses to increase the confidence in their "caseness", they took the union to increase the total number of cases, which will result in either the same (at best) or higher heterogeneity between cases.

Second, Howard et al 2018 removed controls from "ICD10-coded depression" who are cases in "probable depression". As the questions that qualify one for a case or control of "probable depression" were only asked in half the collection centres in UKBiobank, Howard et al 2018 applied more stringent filtering of controls to one half of the collection centres in the UKBiobank (see our Result section "Definitions of depression in

UKBiobank" and Supplementary Methods section "Control of population structure in heritability estimates" for our explanation of this). This creates different ascertainment biases between different collection centres, and creates confounding between population structure and case status.

Third, Howard et al 2018 excluded from both cases and controls those with ICD10 codes for some other mental health conditions: Bipolar (ICD codes F30, F31 or non-cancer illness code 1291), Multiple personality disorder (ICD code F44.8), Schizophrenia / psychosis (ICD codes F2*, or non-cancer illness code 1289). This removed samples from both cases and controls using the same criteria, and hence does not create artificial discontinuities in the liability distribution. However they have not excluded dementia (F00-F09) which may have affected the answering of the questionnaire, or substance abuse (F10-19) which is standard exclusion for MDD studies. In our definition ICD10Dep, we exclude those with codes F00-F31 (dementia, substance abuse, schizophrenia and psychosis, manic episodes and bipolar disorder) from both cases and controls.

Finally, Howard et al 2019 excluded different medication codes from cases and controls. This introduces artificial discontinuities in the liability distribution, making assessment of genetic architecture more difficult (as we explain in Supplementary section "Case enrichment and "cleaned" controls in GWAS").

Prevalence of definitions of depression in UKBiobank

In our analyses of definitions of depression in UKBiobank, we assume that the prevalence of each definition of depression in the population UKBiobank is represented by the prevalence in the dataset. This cannot be true, as not all participants in UKBiobank were asked questions from all categories. Questions for the Symptom-based definition DepAll were asked in only 10 out of 22 assessment centers in UKBiobank (Supplementary Table 4), and CIDI-based definitions LifetimeMDD and MDDrecur were derived from voluntary participation in the MHQ, which has been shown to have a genetic component genetically correlated with that of mental health conditions[6]. In addition, there may be self-report biases and uneven sampling of different demographics.

We carried out three analyses to ensure that the use of observed sample prevalences as population prevalence is unlikely to affect our conclusions.

First, using correction factors we derived using 2011 UK census data[7], we calculated a corrected prevalence of each definition of depression in the UKBiobank, and re-ran all our analyses of h^2_{SNP} using that, with the results shown in Supplementary Tables 13. We find that discrepancies between sample and population prevalences for all definitions of depression we examine in UKBiobank are small, when corrected for regional populations, age and sex (Supplementary Tables 5-7).

Second, we obtained estimates assuming there is a "true" prevalence of 15% for MDD in European populations, as PGC1-MDD[8] had used, and show the results in Supplementary Tables 13. Both results are plotted out together with estimates using the observed sample prevalences derived directly from the number of cases and controls in each definition as population prevalence, (shown in Supplementary Figure 3). While there are some differences in the estimates, they do not qualitatively change our results: minimal phenotyping definitions of depression (GPPsy, Psypsy) show significantly lower h^2_{SNP} than MDD defined with more stringent criteria (LifetimeMDD, MDDRecur).

Finally, we asked if there are is any combination of prevalences we can use to arrive at a conclusion that all definitions of depression in UKBiobank have the same liability scale h2SNP, comparable to the 0.20 found in PGC1-MDD. We show in Figure 3b that there is no such combination: liability scale h2SNP of minimal phenotyping definitions of depression cannot reach a liability scale h2SNP of 0.20 regardless of the prevalence we assume they have in the population.

Control of population structure in SNP-heritability estimates

We performed principal component analysis (PCA) on directly genotyped SNPs from samples in UKBiobank and used PCs as covariates in all our analyses to control for population structure. From the array genotype data, we first removed all samples who did not pass QC, leaving 337,198 White-British, unrelated samples. We then removed SNPs not included in the phasing and imputation and retained those with minor allele frequencies (MAF) >= 0·1%, and P value for violation of Hardy-Weinberg equilibrium $> 10^{-6}$, leaving 593,300 SNPs. We then removed 20,567 SNPs that are in known structural variants (SVs) and the major histocompatibility complex (MHC)[40] as recommended by UKBiobank[73], leaving 572,733 SNPs. Of these, 334,702 are common (MAF > 5%), and from these common SNPs we further filtered based on missingness <0·02 and pairwise LD $r^2 < 0·1$ with SNPs in a sliding window of 1000 SNPs to obtain 68,619 LD-pruned SNPs for computing PCs using flashPCA[74]. We obtained 20 PCs, their eigenvalues, loadings and variance explained, and consistently use these PCs as covariates for all our genetic analyses.

As recommended by the UKBiobank[1], we removed the major histocompatibility complex (MHC) region as well as known structural variants (SVs)[9] before selecting SNPs for the computation of PCs (Methods) which we use for all association and h^2_{SNP} analyses. As a result, there is little control over population structure over these regions in both association testing and h^2_{SNP} estimation. This may lead to false positive associations as well as inflated h^2_{SNP} estimates. We therefore indicated whether each significant association is in MHC and SV regions in Supplementary Table 10, 11, 16 and 17, and use hollow points to represent SNPs in Manhattan plots (Extended Data Figure 3 and Supplementary Figure 5) - the validity of these associations can be followed up with sequencing of regions involved, and does not fall in the scope of this paper.

To check if lack of population structure control over SVs and MHC regions affect h^2_{SNP} estimates, we estimate h^2_{SNP} using LDSC using all SNPs (LDSC-AllSNPs), excluding SNPs in the MHC region on chromosome 6:25-35MB (LDSC-noMHC), and excluding SNPs in the both MHC region and SVs [9] (LDSC-noMHCSVs). In Supplementary Figure 3 we show that while h^2_{SNP} decreases from LDSC-AllSNPs estimates when we remove MHC or/and SVs, the decreases are not significant in any of the definitions of MDD in UKBiobank, and the trend between definitions of MDD remain the same. As such, we conclude that excluding MHC and SVs in the calculation of PCs is unlikely to cause significant biases in estimation of heritabilities of particular or all of the definitions of MDD.

Finally, questions forming the criteria for different definitions of MDD are not all answered by the same individuals in UKBiobank, potentially leading to different levels of cryptic relatedness and population structure among individuals making up cases and controls in different definitions of MDD. For example, questions on cardinal symptoms of MDD in the touchscreen questionnaire, necessary for meeting the criteria for being a case in DepAll, are answered by only those who went to 10 out of 22 assessment centres (Supplementary Table 4).

To ensure we control for population structure adequately for all definitions of MDD in UKBiobank regardless assessment centre, we assessed the per-chromosome heritabilities of all definitions of MDD estimated jointly and separately with BOLT-REML, using a total of 334,681 genotyped SNPs with MAF > 5% and HWE P-value $> 10^{-6}$ across all chromosomes as model SNPs. Difference between the slopes between per chromosome h^2_{SNP} and length of chromosome (approximated with number of SNPs used as model SNPs in each chromosome) in the two models (joint and separate) reveals population structure that induces long-range LD between chromosomes. This is because in presence of population structure h^2_{SNP} attributable to SNPs on one chromosome "leaks" into the estimates of a different chromosome, due to long-range LD, when h^2_{SNP} are estimated separately.

We find that the difference between the two slopes are minimal when using PCs calculated using all White-British samples in UKBiobank, which we used as covariates in h^2_{SNP} estimates and GWAS on the definitions of MDD in UKBiobank (Methods). We show the results in Supplementary Figure 3; we therefore use all-samples PCs in all the h^2_{SNP} estimates and GWAS we report, except for stratified analyses where numbers of samples in each stratum are substantially smaller than the whole UKBiobank White-British cohort where we used definition and stratum specific PCs.

Measure of lifetime trauma

A binary measure of lifetime trauma was derived from self-reported experience of traumatic events from the online mental health follow up questionnaire (data category 145), in order to identify individuals exposed to severe environmental adversities. The online mental health questionnaire for traumatic events consist of 16 questions on childhood, adulthood and lifetime trauma. We have scored individuals as having experienced each traumatic event as "1" and those who have not experienced each traumatic event as "0", as shown in Supplementary Table 12. Of the 16 questions, we have included 12 for derivation of an aggregate "lifetime trauma" measure, the remaining 4 capture the same traumatic events the other questions we have included do, and are hence redundant.

We asked how much each traumatic experience contributes to the risk of developing LifetimeMDD, the CIDI-based definition of MDD in UKBiobank, by jointly modeling their contribution in a logistic regression, along with age, sex, social deprivation (using the Townsend deprivation index), years of education, experience of any traumatic life event in the past 2 years (data field 6145), neuroticism, and total number of traumatic experiences. The odds ratios (ORs) of each traumatic experience on LifetimeMDD is shown in Supplementary Table 12.

Since traumatic events vary in severity, a lifetime trauma score was constructed by weighting each item by their effect size on LifetimeMDD, and summing across all 12 items. As not all questions about traumatic experience are answered by all individuals who took part in the online mental health follow-up, we removed individuals who did not answer more than 3 questions on traumatic experience. We obtained lifetime trauma score for 109,699 individuals, with mean score 1.90 (standard deviation = 2.11). We categorize 33,619 individuals with scores above 2.5 as having experienced significant lifetime trauma (who report a mean of 3.17 traumatic experiences) and those with scores below 2.5 as not having experienced significant lifetime trauma (who report a mean of 0.66 traumatic experiences).

We note the following caveats in our use of self-reported answers to questionnaires to infer level of lifetime trauma. First, in weighting traumatic events based on their effects on LifetimeMDD in creating the measure of lifetime trauma, one can potentially incur biases in genetic associations to LifetimeMDD at genetics variants that contribute to both lifetime trauma and LifetimeMDD when one stratifies individuals in LifetimeMDD by lifetime trauma. However, this bias will likely be small, as the weighted lifetime trauma score is highly correlated with the number of traumatic experiences an individual self-reports ($r2=0.92$, $p <10^{-16}$), and this self-report is assumed to be independent of LifetimeMDD (see second caveat). Moreover, even if present, this bias will not extend to other definitions of MDD in UKBiobank acquired through independent questionnaires.

Second, as both questionnaires on traumatic events and CIDI-based MDD symptoms (used for specifying LifetimeMDD) are on the same online mental health follow up assessment, how one answers one questionnaire may affect how one answers the other, potentially incurring errors in retrospective recall. This is an unavoidable problem in UKBiobank given the structure of the questionnaire, and as such here we assume that the errors incurred are negligible. In addition, as the online mental health follow-up is conducted a year or two after one takes part in the initial assessment through the touchscreen questionnaire, there should be little to no effects of retrospective recall errors on all other definitions of MDD in UKBiobank, which we derive from answers to questions in the touchscreen questionnaire.

Epidemiological analysis of risk factors for MDD

We assess the effects of known risk factors for MDD on the different definitions of MDD in UKBiobank; for each binary or quantitative risk factor, we estimatd its odds ratio (OR) for each definition of MDD using logistic regression, correcting for UKBiobank collection centers (data field 54, as factors), as well as years of education (data field 845, quantitative), age (data field 21022, quantitative) and sex (data field 31, binary) unless one of three factors is being tested. The binary risk factors we tested are:

1. Age: data field 21022; dividing individuals into those < 60 years old and those >= 60

2. Sex: data field 31; dividing individuals into males and females
3. lifetime trauma: data category 145 for "Traumatic events reported within the on-line mental health questionnaire"; we calculated a weighted measure of traumatic events, dividing individuals into those who have weighted measure = 1 and those with weighted measure = 0.

The quantitative risk factors we tested are:

1. neuroticism: data field 20127 for "12 neurotic behaviour domains as reported from fields 1920, 1930, 1940, 1950, 1960, 1970, 1980, 1990, 2000, 2010, 2020 and 2030 from the touchscreen questionnaire at baseline"
2. social deprivation: data field 189 for townsend deprivation index (TDI) calculated for per individual just before baseline assessment)
3. years of education: data field 845; for age one stopped continuous full-time education, from which we infer years of continuous education received by each individual assuming starting age of 6.

For quantitative risk factors we report ORs for per SD increase in the measure. The UK Biobank cohort contains more women than men (the female to male ratio is 1.16 to 1), with more younger women than men (there are 6% more women than men younger than 60, compare to 2% older than 60) and is more educated among the young than the old (those with more than 10 years of education form 42.5% of those younger than 60, compare to 28.4% among those older than 60). Thus, in each analysis we included age, sex and number of years of education as covariates unless they are the risk factors tested (together with collection center).

Potential confounding from self-ascertainment bias

A recent preprint has shown that voluntary participation in the MHQ has a genetic component genetically correlated with that of mental health conditions[6]. This raises the concern that difference between definitions of depression in their genetic architecture are in fact driven by genetic differences between those who answered this questionnaire and those who did not. In fact, this is a more general problem that affects all phenotypes in the UKBiobank, all of which are dependent on voluntary self-reporting. Using the derivation of CIDI-based definitions of MDD LifetimeMDD from the MHQ as an example, we explain how we may understand self-ascertainment bias.

First, if the self-ascertainment bias to participate in the MHQ is directly driven by MDD (the underlying condition rather than definitions of MDD from the self-reports), where those with MDD are more likely to participate, then the prevalence of cases of MDD will be higher among those who have taken the MHQ. This is consistent with what we observe with our CIDI-based definitions of MDD in UKBiobank LifetimeMDD, both of which have much higher case prevalence than expected (0.243 and 0.173 respectively). In this scenario, the ascertainment bias for MDD from using data from MHQ is akin to the ascertainment in any GWAS where cases are oversampled (the vast majority of disease GWAS to date).

This does not violate assumptions used in estimation laid out in section "Case enrichment and use of "clean" controls in GWAS" – in particular it does not violate assumption 4 "The probability for a case or a control to be selected for the study, from all cases and all controls in the population, depends only on their phenotype and not any other factors". As explained in the section "Comparison of methods of heritability and genetic correlation estimation", PCGCs can account for the over-sampling of cases better than other methods. For this reason we use it for estimation of h^2_{SNP} of all definitions of depression, as well as to estimate rG between them.

Second, the self-ascertainment bias to participate in the MHQ may not be driven by MDD itself, but by conditions genetically correlated with MDD, either alone or in combination with MDD. In this scenario, those with MDD are more likely to participate, and those with conditions correlated with MDD (but who are not cases of MDD) are also more likely to participate. What biases result from this scenario depends on whether

participation in the MHQ is independent of one's ability to answer questioning relating to MDD symptoms accurately.

If we assume participation in the MHQ *does not* affect one's ability to answer questions relating to MDD symptoms, then our bias will lie in the controls – these controls contain more individuals with conditionally genetically correlated with MDD (A). If we believe participation in the MHQ *does* affect one's ability to assess whether one has MDD symptoms, then a bias may be present in both cases and controls. This bias may be consistent between cases and controls (B), or different between cases and controls (C). B does not violate any assumptions outlined in "Case enrichment and use of "clean" controls in GWAS", and hence does not cause problems in h^2_{SNP} estimation – this scenario can be seen as h^2_{SNP} of LifetimeMDD is estimated in a different population as that of other definitions of depression in UKBiobank. A and C are problematic in the same way – they violate assumption 4 "The probability for a case or a control to be selected for the study, from all cases and all controls in the population, depends only on their phenotype and not any other factors", and introduce a correlation between defined depression phenotype and the underlying condition that causes the self-ascertainment bias to participate in the MHQ. If this underlying cause has a genetic component, then this genetic component can appear to have effects on LifetimeMDD too. No methods for assessing h^2_{SNP} to date can account for this adequately.

However, we can ask if genetic effects we observe in LifetimeMDD are driven by this underlying cause using the Mendelian Randomization (MR) framework. If MR shows a significant correlation between genetic effects on MHQ participation and that on LifetimeMDD, then we can conclude this is a significant problem, and we cannot trust results from LifetimeMDD. As such, we obtained 25 independent variants (LD r2 <1) from Adams et al 2019, of which 16 are SNPs with INFO scores above 0.9 in the UKBiobank that we include in GWAS on our definitions of depression (Supplementary Table 8).

We performed MR using the MendelianRandomization R package[10], with the following estimators: simple median, weighted median, inverse-variance weighted (IVW)[11] and MR-Egger[12], as shown in Supplementary Table 9. None of the estimators shows significant causal effect of MHQ on any definition of depression (threshold P-value = 0.05/36 = 0.0016). As there are two outlier SNPs with high effects on answering of MHQ (exposure, as shown on Supplementary Figure 4) that may bias our results, we performed the analysis again removing the two SNPs, and still found no significant causal effect of answering the MHQ on any definition of depression (Supplementary Figure 4, Supplementary Table 9). Further, without a significant causal effect from any of the estimators, the MR-Egger intercept cannot be used to infer pleiotropy[13]. We find no support for the view that the genetic factors influencing whether one answers the MHQ has an impact on our findings on the definitions of depression.

Case enrichment and use of "clean" controls in GWAS

Many GWAS studies of MDD and of other conditions apply additional filters to the diagnostic criteria to improve power of association. One such additional filter is to remove controls which nearly qualify as cases of the disease by the same set of diagnostic criteria, or qualify as cases of the disease of interest by a different set of diagnostic criteria. For example, in Howard et al 2018[3], controls in "ICD10-coded depression" who qualified as cases of "Probable depression" were excluded from the GWAS (we explore this further in the next Supplementary Methods section). We refer to this approach as using "clean" controls.

Use of "clean" controls does increase power in GWAS. In addition to performing GWAS using all cases and controls for each definition of depression in UKBiobank we define in this paper, we obtained "clean" controls, which are not cases in any other definition of depression, and performed GWAS using these "clean" controls. We obtain more GWAS hits than using all cases and controls (Supplementary Figure 3, Supplementary Table 10-11). However, we do not use "clean" controls for any analysis of genetic architecture and comparison between definitions, for two reasons.

First, our paper focuses on comparing different strategies of phenotyping, and therefore only considered phenotypes that can be obtained with information taken at one time point. Given we are effectively "simulating" GWAS studies that only collect 1 piece of information at a time, we should not be able to arrive at "clean" controls.

Second, using "clean" controls introduce artificial discontinuities in the liability distribution that are difficult to account for[14]. Under the liability threshold model, liability to a disease in a population is contributed by both genetic and environmental factors. The binary case/control status is assigned by defining a liability threshold corresponding to the observed disease prevalence, where everyone above the threshold would be classified as cases, and everyone below it would be controls. This forms the basis for the following assumptions used in estimating liability scale SNP-heritability (h^2_{SNP}) with the conversion from observed scale proposed by Dempster and Lerner[15] and appropriated for h^2_{SNP} estimation using REML by Lee et al [16], which is later adopted for BOLT-REML[17], summary statistics based method LDSC[18], and exact methods for binary traits PCGC[19] and PCGCs[20].

1. The liability is normally distributed. A corollary of this is that unmeasured environmental factors induce a normally-distributed effect on the phenotype that is independent from the normally distributed effect exerted by the genotypic factors.
2. Each causal SNP exerts a linear effect on the phenotype
3. Each covariate exerts a linear effect on the phenotype
4. The probability for a case or a control to be selected for the study, from all cases and all controls in the population, depends **only** on their phenotype and not any other factors

If we had used a "clean" set of controls (those who would come up negative on criteria for all definitions of depression) for GWAS on each definition of depression, we would be violating assumption 4 and introducing an artificial discontinuity in the liability distribution. This bias our estimates of h^2_{SNP} and all other measures of genetic architecture based on it.

Comparison of methods of SNP-heritability and genetic correlation estimation

Many methods have been developed to estimate narrow sense SNP heritability (h^2_{SNP}) from either whole-genome SNP data[17,19,21,22] or summary statistics of association tests [18,20,23] across the whole genome, and the sensitivity of h^2_{SNP} estimates to assumptions in different models employed by the different methods have been discussed and reviewed extensively in the past few years[24,25].

For all the h^2_{SNP} estimates in our analysis we use the phenotype-correlation-genotype-correlation (PCGC) approach, an adaptation of Haseman-Elston regression. We prefer this method because it produces unbiased estimates of h^2_{SNP} and genetic correlation (rG) for case-control phenotypes[19,20] in the presence of covariates of large effect, such as sex and age. As mentioned in the Results section as well as the Supplementary Methods section "Prevalence of definitions of MDD in UKBiobank", cases and controls for some or all of the definitions of depression we use may not represent the full liability distribution of the population. Instead they may represent a potentially skewed or discontinuous proportion of it. For example, LifetimeMDD is derived from the MHQ, which is voluntarily answered by a non-random proportion of individuals in UKBiobank, and the answering of the MHQ has been shown to be genetically correlated with mental health traits[6]. When this is the case, the second assumption we outlined in the Supplementary methods section "Case enrichment and use of "clean" controls in GWAS" is violated – the effects of the unmeasured environmental factors on the phenotype of interest (definitions of depression) are potentially no longer independent of the effects of the genetic factors. This leads to downward bias in h^2_{SNP} estimates from LDSC and REML-based methods, even when the relevant covariates (which we assumed to be PCs in this case, accounting for population structure in each definition of depression) are used in GWAS[19,20]. Such bias will propagate to other measures of genetic architecture based on h^2_{SNP}, such as rG. As Weissbrod et al 2018[20] explained, this is a problem that can be circumvented by "regressing the omitted

covariates out of the genotypes and correcting the individual-level affection cutoffs prior to parameter estimation or to computing summary statistics", as is performed in PCGCs.

As such, we use the PCGCs[19,20] framework, generating summary statistics for definitions of MDD in UKBiobank in our study which can be reused for estimation of genetic correlation with other phenotypes from other cohorts processed the same way.

We note, however, that previously published estimates of h^2_{SNP} of MDD[3,8,26-28], are mostly generated using LDSC[18] if they were estimated from GWAS summary statistics, or either GCTA[22], LDAK[21], or BOLT-REML[17] if they were estimated from individual level genotypes. All estimate h^2_{SNP} of case-control traits on the "observed scale" under a quantitative trait framework, and apply a correction factor to results to convert them to a "liability scale" to account for the ascertainment of cases in case-control studies. The same applies when estimating rG.

In Supplementary Table 13, we show the h^2_{SNP} estimates of each definition of MDD in UKBiobank using PCGCs[19,20]., LDSC[18], and BOLT-REML[17]. For both PCGCs and LDSC, we use 8,968,716 imputed SNPs with MAF > 5% in our analysis (Methods), while for BOLT-REML we use 334,681 genotyped SNPs with MAF > 5% and HWE P-value > 10^{-6} as model SNPs. For results from LDSC and BOLT-REML, we use LD scores calculated on all imputed SNPs in UKBiobank, using LDSC as reference, and convert the h^2_{SNP} estimates on the observed scale to liability scale specifying the prevalence of each definition of MDD in UKBiobank as shown in Supplementary Table 8.

Results from all three methods show the same trend - the CIDI-based definitions LifetimeMDD and MDDRecur show the highest h^2_{SNP} estimates while the help-seeking based definitions GPpsy and Psypsy, as well as their no-MDD components GPNoDep and PsyNoDep, show the lowest h^2_{SNP} estimates. While LDSC and BOLT-REML estimates are highly similar to each other, PCGCs estimates are higher than both of them, consistent with expectations of downward bias in h^2_{SNP} estimation of case-control traits using LDSC and REML due to handling of covariates.

For comparison of h^2_{SNP} estimates from our study with previously published estimates using LDSC, we show in Supplementary Figure 6 that the CIDI-based definitions LifetimeMDD and MDDRecur have heritabilities closer to LDSC h^2_{SNP} estimates of MDD in CONVERGE[26] and PGC1-MDD[8], while help-seeking based definitions GPpsy and Psypsy have estimates closer to that in similarly defined, minimal phenotyping based MDD in 23andMe[27].

For PCGCs, we show estimates of genetic variance and its standard error for every definition of depression in UKBiobank. "Genetic variance" is variance attributable to genetics over total phenotypic variance (referred to as "marginal heritability" in Weissbrod et al 2018[20]), and is the measure comparable measure to h^2_{SNP} from BOLT-REML and LDSC (Supplementary Table 13). For completeness, we also show estimates of "conditional heritability", which is genetic variance divided by the total liability variance, and which also includes variance introduced by fixed effects (in this case, genotype PCs and genotyping array, Supplementary Table 13).

We also compared the estimation of rG between definitions of MDD using PCGCs and LDSC. In Supplementary Figure 6 we show the genetic correlation between LifetimeMDD, the CIDI-based definition, with all other definitions of MDD in UKBiobank estimated using LDSC (Figure 3b shows the PCGCs estimates). LDSC estimates show a similar trent to those from PCGCs, though both point estimates are higher across the board and standard errors are larger than from PCGCs, making most estimates not significantly different from 1. This is consistent with the expectation that LDSC may over-estimate genetic correlations due to mishandling of covariates and overlap of samples[20]. Overestimates of rG between definitions of MDD (not significantly different from 1) may send the misleading message that the genetic architectures in different definitions of MDD, even those on opposite ends of the spectrum in terms of case criteria, are not significantly different from each other. This obscures important true genetic differences between different definitions of MDD.

Stratification of definitions of depression by environmental risk factors

We stratified samples from definitions of MDD in UKBiobank by environmental risk factors in the following ways. We estimate h^2_{SNP} in each strata of samples using PCGCs (Methods). Results are shown in Supplementary Table 14.

1. by age: data field 21022; dividing individuals into those < 60 years old and those >= 60
2. by sex: data field 31; dividing individuals into males and females
3. by lifetime trauma: data category 145 for "Traumatic events reported within the on-line mental health questionnaire"; we calculated a weighted measure of traumatic events, dividing individuals into those who have weighted measure >= 2.5 and those with weighted measure < 2.5
4. by neuroticism: data field 20127 for neuroticism score; dividing individuals into those who score >= 5 and those who score < 5
5. by social deprivation: data field 189 for Townsend deprivation index (TDI); dividing individuals into those with TDI <0 and those with TDI >=0
6. by years of education: data field 845; dividing individuals into those with years of education >= 11 and < 11).

Using the h^2_{SNP} estimates and standard errors from PCGCs, we performed t-tests on the h^2_{SNP} from the strata in each stratification, and ask whether they are significantly different from 0 at p < 0.05, using a two-tailed test and correcting for 49 stratifications. None of the difference between strata, from any definition of MDD and stratification, is significant, though the method is underpowered as compared to other methods that require the use of individual level genotypes[29].

Simulations of effects of misdiagnosis and misclassification on SNP-heritability estimates

In this section we explore whether minimal phenotyping definitions of MDD represent milder forms of the disease (those with lower liability) that do not qualify for CIDI-based definition of MDD, or whether they contain misdiagnosis of those without the disease as cases.

We perform simulations to show the effects of misdiagnosis and misclassification on h^2_{SNP} estimates, and in turn, whether they may be the cause of lower h^2_{SNP} estimates in the minimal phenotyping definitions of MDD. We adopt the theoretical framework of the liability threshold model, where every individual has a normally distributed liability value for a trait such that case subjects of the trait are individuals whose liability exceeds a given cutoff[15]. The cutoff for the liability was determined as the 1-K_i percentile of the simulated liabilities, where K_i for the i-th simulated trait is set as the prevalence of cases. To simulate a biobank sample (which is assumed to be representative of the population), we do not ascertain for cases.

Using array genotypes at 344,184 SNPs (LD < 0.5, MAF > 5%, HWE P-value > 10e-6) in 25,000 random individuals from UKBiobank who are White-British (Methods), we used LDAK[21,30] to simulate pairs of traits $y_{i,1}$ and $y_{i,2}$ with genetic correlation rG_i, where for each i in $i \in \{1..10\}$: 5000 causal SNPs are picked uniformly at random to contribute a total h^2_{SNP} for $y_{i,1}$ and $y_{i,2}$ of $h^2_{i,1} = h^2_{i,2} = h^2_i$ using the model $Y = \sum \beta_j X_j + e$, where β_j is the effect size of X_j, the jth causal SNP, and e is Gaussian-distributed noise. Effect size at each SNP X_j is sampled under the Model $\beta_j \sim N\left(0, \left[f_j\left(1 - f_j\right)\right] - 1\right)$, where f_j is the MAF of X_j.

The LDAK command we use is as follows:

ldak5.linux --make-phenos traitpair$i.h2$h2i.rg$rGi --bfile $bfile --ignore-weights YES --power -1 --num-causals 5000 --num-phenos 2 --her $h2i --bivar $rGi

Where $i \in \{1..10\}$, $h_i^2 \in \{0.2, 0.4, 0.6, 0.8\}$, $rG_i \in \{0, 0.2, 0.4, 0.6, 0.8, 0.95\}$

In the first set of simulations, we show that including individuals with lower liabilities to a disease (trait) as cases (increasing prevalence of cases through lowering the liability cutoff) would not have an effect on liability scale h^2_{SNP} estimates of the trait. We estimate the liability scale h^2_{SNP} of each trait using the --pcgc option in LDAK appropriate for binary traits, accounting for the prevalence of cases K_i used. As we both do not ascertain for cases, and do not simulate covariates with effects on the traits, h^2_{SNP} estimates from the simulations do not suffer from downward estimates in REML presented previously for case-control traits[20] when converted to the liability scale[15,19]. As such, using both --reml with --prevalence and --pcgc options give the same liability scale h^2_{SNP} estimates on the simulated traits. Extended Data Figure 1 shows the h^2_{SNP} estimates of traits with heritabilities $h_i^2 \in \{0.2, 0.4, 0.6, 0.8\}$ for $i \in \{1..10\}$, where we shift the prevalence K_i from 0.1 to 0.5, and recover the simulated h^2_{SNP} exactly regardless of K_i. While this is well-known, it refutes the misconception that minimal phenotyping definitions of MDD have lower h^2_{SNP} than CIDI-based definitions because they contain individuals with lower liabilities to MDD.

In the second set of simulations, we show that misdiagnosis of controls as cases lowers h^2_{SNP}. At a constant liability threshold corresponding to $K_i = 0.2$, if we identify all individuals above liability threshold correctly as cases, but identify random controls as cases such that the percentage of misdiagnosis cases ranges from 0% to 50% of all cases (thereby increasing apparent case prevalence), then liability scale h^2_{SNP} (corrected for the apparent prevalence) decrease as a result (Extended Data Figure 1). This decrease is consistent with the high prevalence and low h^2_{SNP} we observe in minimal phenotyping based MDD in UKBiobank and 23andMe[27] (Figure 3a, Supplementary Figure 6). We note that our simulations do not misidentify true cases as controls (in other words, we have a sensitivity of 100% for true cases, while having a false discovery rate of cases ranging from 0% to 50%); in realistic settings, it is possible sensitivity to true cases will decrease as collection criteria becomes less stringent. If we lower the sensitivity, the h^2_{SNP} estimates are likely to decrease further.

However, the above scenario must not be the only explanation for the lower h^2_{SNP} in minimal phenotyping based MDD. Genetic correlation between definitions of MDD should not differ if all genetic factors are shared and effects were only lower in some definitions due to noise (Figure 3b). Hence, we hypothesize minimal phenotyping definitions of MDD may in fact contain cases of other conditions that are misclassified as MDD. We simulate misclassification of cases from a genetically correlated disease to find out if misclassification may result in a decrease in h^2_{SNP} consistent with the lowered h^2_{SNP} estimate in minimal phenotyping definitions of MDD.

We first correctly identify all individuals above liability threshold for prevalence $K_{i,1} = 0.2$ in $y_{i,1}$ ($h^2_{i,1} = 0.4$) as cases of $y_{i,1}$. Then, we misclassify 10% to 50% of cases of genetically correlated $y_{i,2}$ ($h^2_{i,2} = 0.4$, prevalence $K_{i,2} = 0.2$) as cases of $y_{i,1}$, hence increasing the apparent case prevalence of $y_{i,1}$. The two traits have genetic correlation $rG_i \in \{0, 0.2, 0.4, 0.6, 0.8, 0.95\}$. As shown in Extended Data Figure 1, we find that increasing the percentage of misidentification decreases liability scale h^2_{SNP} of $y_{i,1}$ (corrected for the apparent prevalence) if rG_i is small, but can inflate liability scale h^2_{SNP} if rG_i is large (>=0.6). This inflation decreases with increase in h^2_{SNP} of both traits (Extended Data Figure 2). This analysis shows that as long as two traits are completely heritable, and there are environmental contributions, misclassifying cases of one as cases of the other would lead to erroneous estimates of h^2_{SNP}, even at very high genetic correlations.

As genetic correlation between definitions of MDD and other psychiatric conditions are low (maximum genetic correlation with neuroticism at a mean of 0.67 among all definitions of MDD, Supplementary Table 18, Figure 4a), and genetic correlation between CIDI-based definition of MDD (LifetimeMDD) and those without MDD (GPNoDep, making up 30% cases in minimal phenotyping definition of MDD GPpsy) is 0.58 (se=0.078), most of the potential misclassification could have come from conditions with genetic correlation with MDD lower than 0.6 and led to downward bias of h^2_{SNP} observed in minimal definitions of MDD in UKBiobank.

In summary, our simulations are consistent with a model where the lower h^2_{SNP} in minimal phenotyping based

MDD is not due to lowering liability threshold for case definition in MDD, but a consequence of potentially both misdiagnosis of those who do not have MDD as cases, and misclassification of those with other conditions as cases (and the misidentification of true cases as controls, not simulated).

Meta-analysis between PGC29 and LifetimeMDD

We obtained summary statistics of meta-analysis of GWAS on 29 MDD cohorts in the Psychiatric Genomics Consortium (PGC29, N = 42,455) through the MDD Working Group of the Psychiatric Genomics Consortium (PGC-MDD), reported in Wray et al 2018 [5]. Prior to meta-analysis with LifetimeMDD (N = 67,171), we removed all INDELs, as well as SNPs with MAF < 5% and imputation INFO score < 0.9, leaving 5,828,030 SNPs. We use this set of summary statistics for estimation of h^2_{SNP} with LDSC, as well as for enrichment analyses in LDSC-SEG[51]. We then performed a meta-analysis between the filtered summary statistics of PGC29 with those of LifetimeMDD using METAL[81] using the SCHEME STDERR. We removed those SNPs at which no meta-analysis was performed due to their absence in either dataset. The final meta-analysed data contained summary statistics at 4,693,521 SNPs for a total sample size N = 109,626, which we used for estimation of h^2_{SNP} with LDSC, as well as for enrichment analyses in LDSC-SEG.

LDSC-SEG analysis of tissue-specific enrichment of h^2_{SNP}

The LDSC-SEG analysis tests whether the h^2_{SNP} of a disease is enriched in regions surrounding genes with the highest specific expression in a given tissue[31]. In a meta-analyses of several depression studies Wray et al 2018 demonstrated significant enrichment of h^2_{SNP} in regions surrounding genes whose expression is highest in CNS tissues, including the frontal cortex, anterior cingulate cortex, putamen, nucleus accumbens, hippocampus and substantia nigra[32].

We tested whether different definitions of MDD in UK Biobank showed similar enrichment, by performing the same LDSC-SEG analysis on all definitions of depression in UKBiobank, as well as all psychiatric conditions included in the PGC Cross Disorder Working Group (including MDD (PGC1-MDD), schizophrenia (SCZ), bipolar disorder (BIP), attention deficit hyperactive disorder (ADHD), and autism (AUT), as listed in Supplementary Table 1), both smoking and neuroticism in UKBiobank (Extended Data Figure 3, Supplementary Tables 16-17), and the minimal phenotyping definition of depression 23andMe[27] (Supplementary Table 1). We found that other psychiatric conditions including SCZ, BIP, neuroticism and smoking all show CNS enrichment of h^2_{SNP}, along with the minimal phenotyping definition of depression in 23andMe.

We found that the strictly defined definitions of MDD in UKBiobank (LifetimeMDD), as well as MDD defined by structured interview in PGC1-MDD [8], do not show CNS enrichment, while minimal phenotyping definitions of depression GPpsy does. This may seem counter-intuitive, given a CNS enrichment is expected for MDD. We therefore investigated the potential reasons for differences between tissue-specific enrichments of h^2_{SNP} between strictly defined MDD (LifetimeMDD and PGC1-MDD) and minimally defined depression (GPpsy and 23andMe).

First, it is possible the sample size for strictly-defined LifetimeMDD (16,301 cases and 50,870 controls) or PGC1-MDD (16,301 cases and 50,870 controls) was too small to provide enough statistical power for a discovery of enrichment. We therefore obtained summary statistics of PGC29[32,33] (16,823 cases and 25,632 controls), and performed a meta-analysis between it and LifetimeMDD to boost the sample size for strictly-defined MDD. We observed enrichment in PGC29 as shown in Extended Data Figure 4. A meta-analysis of LifetimeMDD and PGC29, however, does not, suggesting differences in genetic architecture between MDD derived from MHQ self-reporting and structured interviews. On one hand, MHQ based self-reporting may capture sub-clinical MDD; on the other, CIDI-based diagnostic criteria may not be strictly adhered to in the collection of all cases in PGC29. As shown in Supplementary Table 21, cohorts in PGC29 have varying percentages of cases fulfilling DSM diagnostic criteria, in addition to heterogeneity in ascertainment strategies and genetic outcome among cohorts in PGC29[33]. This heterogeneity is reflected in differences in individual

cohort h^2_{SNP} [33], as well as the lower h^2_{SNP} of PGC29 compared with PGC1-MDD (Supplementary Figure 6). These results show that tissue-specific enrichment of heritability may be affected by many factors, including sample size and specificity in phenotyping approaches, and lack of CNS enrichment in one strictly defined MDD phenotypes does not mean that there is no CNS enrichment in genetic effects on MDD.

Second, CNS enrichment cannot indicate relevance or specificity of genetic effects to any particular disease. While LifetimeMDD (16,301 cases and 50,870 controls) shows no CNS enrichment, GPNoDep (8,632 cases and 49,493 controls, fewer than LifetimeMDD) does. When we down-sampled all definitions of depression in UKBiobank to N = 50,000, each with a case prevalence of 0.15 (N cases = 7,500) to ensure all definitions have the same statistical power, only GPNoDep still showed significant CNS enrichment (Extended Data Figure 4). Cases in GPNoDep makes up 30% of cases in GPpsy, and may drive genetic signals that are discovered in GPpsy. It has a low h^2_{SNP} than both strictly defined MDD and minimal phenotyping definitions of depression, consistent with a higher levels of mis-diagnosis and misclassification among its cases (Figure 3, Extended Data Figure 1-2, Supplementary Methods). Sources of such mis-diagnosis and misclassification in GPNoDep, and by extension GPpsy, could potentially be neuroticism and smoking, both of which demonstrate CNS enrichment. Consistent with this hypothesis, GPNoDep, neuroticism and smoking replicate GWAS hits of GPpsy, and mirror effect size distributions of GWAS hits of GPpsy (Figure 6). As such, it is also possible that the CNS enrichment shown in depression defined in 23andMe is driven by similarly non-specific effects, given all of its GWAS hits are replicated in neuroticism and smoking too (Extended Data Figure 3). These results show that the presence of significant CNS enrichment of heritability is not specific to a particular disease, and hence cannot be used to demonstrate the biological relevance or specificity of genetic effects found in a GWAS for any particular definition of depression.

In summary, whether a disease phenotype shows an enrichment of h^2_{SNP} in a particular expected tissue depends on a variety of factors including sample size, phenotyping strategy, and heterogeneity, in addition to whether the expected tissue truly harbor enrichments of h^2_{SNP} for the disease. While it is useful to examine tissue-specific enrichments to understand the genetic architecture of a disease, the measure cannot be used in turn to validate a particular phenotype due to its non-specificity.

Out-of-sample prediction of MDD in PGC cohorts

To assess the relative power of the different definitions in UK Biobank to index MDD, we carried out an out-of-sample prediction using data from the MDD working group of Psychiatric Genomics Consortium. We obtained access to individual level genotype and phenotype data from 25 out of the PGC29. The 4 cohorts we did not apply to permission to are pharmaceutical company cohorts. Of the 25 cohorts we did obtain access to, 2 have fewer than 500 samples and were left out from out analyses due to low sample size. We detail this information in Supplementary Table 20.

Of the 23 MDD cohorts we used, 20 recorded endorsement of DSM-V criteria A for MDD from structured interviews. We assessed the percentage endorsement of each DSM-V criteria A symptom in these 20 cohorts, as well as the total number of symptoms endorsed per individual, per cohort (Supplementary Figure 7). We found that not all individuals indicated with a case status met the DSM-V A criteria for a "case" of MDD. We report the percentage of "DSM-MDD Cases" among indicated cases in the 20 cohorts in Supplementary Table 20.

We then obtained PRS using GWAS on each definition of depression using the Ricopili pipeline[34] (Methods), and compared the predictive power of PRS derived from different definitions of depression at each P-value threshold, where $P \in \{1e^{-4}, 0.001, 0.01, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 1\}$. This is done instead of choosing the best P-value threshold per definition of depression, because our aim is not to achieve the best prediction, but to compare the genetic effects and their predictive power between the definitions of depression in the most unbiased way. We assess the prediction accuracy in terms of Nagelkerke's r2 (NKr2), area under the curve (AUC) of true positive against false positive rates, and variance of the MDD disease status explained by the PRS.

If the predictive power of PRS in each definition of depression in UKBiobank was specific to MDD, then greater percentages of DSM-MDD cases in the target PGC cohorts should give a higher prediction accuracy. If instead the PRS of the definition in question was not specific to MDD, then the percentages of DSM-MDD cases in the target PGC cohorts should not be expected to affect its prediction accuracies. We therefore assessed the specificity of PRS from each definition of depression in UKBiobank to MDD, by asking if it gives better predictions in PGC cohorts containing higher percentages of DSM-MDD cases. This is true across all P value thresholds for strictly defined, CIDI-based LifetimeMDD (Figure 7, Supplementary Table 22). As there is little predictive power across all definitions of depression at P-value thresholds 10^{-4} and 0.001, we do not show results at these thresholds for this analysis.

The apparent percentage of "DSM-MDD Cases" and PRS prediction accuracy in each cohort may be explained by the way its data was collected. For example, mmi2 and mmo4 used a questionnaire for assessing lifetime MDD in which some questions were not available and for other questions a choice had to be made about dichotomisation of the ordinal responses; a different choice of dichomisation would give a different result. As such, they have lower apparent percentage of "DSM-MDD Cases". gep3 is only cohort with non-screened controls[33] and may therefore give lower prediction accuracy. In contrast, nes1 has super-screened controls and therefore tends to give high out of sample prediction. In general, community-based cohorts are likely to have lower percentage of "DSM-MDD Cases", while they also have lower proportions of cases. For the same liability variance explained, cohorts with lowest case prevalence in the sample have lowest NKr2. We therefore present AUC as the measure to compare between cohorts.

Effect of Sample size and specificity on prediction power

The key dilemma facing researchers is whether there is more power from allowing a larger sample size through allowing more minimal phenotyping. We first performed the out-of-sample prediction analysis on the full sample size for each definition of depression in UKBiobank, and as expected, at a much larger sample size, minimal phenotyping, help-seeking based GPpsy predict much better than other definitions (Figure 7a, Supplementary Table 21).

We therefore asked if the high observed predictive power for GPpsy (at full cohort N=332,629) can be completely explained by its great sample size. Following Turley et al., 2018[35], the expected predictive power of the PRS from GPpsy is

$$E(R_k^2) = \frac{(h^2)^2}{h^2 + V_k}$$

where h^2 is the SNP heritability of the trait, and V_k is the variance of the normally distributed estimation error for individual polygenic scores

$$e_{k,i} \sim N(0, V_k)$$

in individual i, for each polygenic score $k \in \{GWAS_N\}$, where N is the effective sample size in GWAS. For a binary case-control phenotype, $N = 4/(1/N_{cases} + 1/N_{controls})$. As V_k is inversely proportional to N, $E(R_k^2)$ increases with increasing N.

To obtain polygenic risk scores (PRS) for each definition of depression in UKBiobank without confounding from power differences due to sample sizes, we down-sampled all definitions to a constant sample size of 50,000 and case prevalence of 0.15 through randomly sampling 7,500 cases from all cases, and 42,500 controls from all controls in each definition.

From Figure 7a and 7b we can see that an increase in sample size from $N_{DS} = 4/(1/7500 + 1/42500) = 25500$ (down-sampled, DS) to $N_{FC} = 4/(1/113260 + 1/219362) = 298777$ (full cohort, FC) resulted in a

great increase in the predictive power of PRS from GPpsy. To find the relationship between increasing N and power increase in GWAS and prediction, we use the relationship between N and mean Chi-square $(\overline{\chi^2})$ statistic from GWAS. χ^2 statistic of SNP j with LD score l_j is related to N by

$$E(\chi_j^2 \mid l_j) = \frac{Nh^2 l_j}{M} + Na + 1$$

Where M is the total number of SNPs for which h^2 is defined, and a is the variance due to biases such as population structure. $E(\chi_j^2 \mid l_j)$ scales with N if M and a are constant.

$$\frac{N_{FC}}{N_{DS}} \propto \frac{\overline{\chi^2}_{FC} - 1}{\overline{\chi^2}_{DS} - 1}$$

We found that across all definitions of depression, $\frac{\overline{\chi^2}_{FC} - 1}{\overline{\chi^2}_{DS} - 1}$ is indeed highly correlated with $\frac{N_{FC}}{N_{DS}}$ (Pearson r2 = 0.999, P = 5.50 x 10^{-7}). $\frac{N_{FC}}{N_{DS}}$ has an effect of beta = 1.27 (se = 0.02) on $\frac{\overline{\chi^2}_{FC} - 1}{\overline{\chi^2}_{DS} - 1}$, as shown in Extended Data Figure 7.

We can therefore obtain theoretical V_{FC} for GPpsy from V_{DS} (which we can obtain using known h^2 and NKr2 for down-sampled GPpsy)

$$V_{FC} = V_{DS} \times 1.27 \frac{N_{DS}}{N_{FC}}$$

And obtain theoretical expected predictive power of the PRS from GPpsy at full cohort N_{FC}

$$E(R_{FC}^2) = \frac{(h^2)^2}{h^2 + V_{FC}}$$

If the high predictive power of GPpsy can be completely explained by its large sample size, the theoretical expected predictive power $E(R_{FC}^2)$ should be roughly equal to that we obtain using real data. We see that this is true for GPpsy, where $E(R_{FC}^2)$ = 0.0185 and NKr2 for full cohort GPpsy = 0.0172.

We performed this analysis on all definitions of depression in UKBiobank, and found that for each definition, their increase in predictive power can be predicted and accounted for by the increase in N, as shown in Extended Data Figure 7. The Pearson correlation between predicted and actual NKr2 across all definitions was 0.989 (P = 4.46 x 10^{-5}).

As such, the higher predictive power of GPpsy in Figure 7a (as compared to that in Figure 7b) can be explained entirely by its larger sample size.

We then asked what effective sample sizes other definitions of depression would need to achieve the same predictive power as GPpsy. We calculated their increase in predictive power for N_x where $x > 25{,}500$ and N_{DS} where $DS = 25{,}500$. We obtained the predicted NKr2 for $1.27 \frac{N_x}{N_{DS}} \in \{1 \dots 15\}$, and found that strictly defined LifetimeMDD needs a smaller $1.27 \frac{N_x}{N_{DS}}$ to achieve the same NKr2 as GPpsy: while N_x= 274677 for a NKr2 of 0.0172 in full-cohort GPpsy (actual N = 298677 for an actual sample size of 332,629), a smaller N_x= 129106 needed to achieve the same Nkr2 for LifetimeMDD.

Supplementary Figures
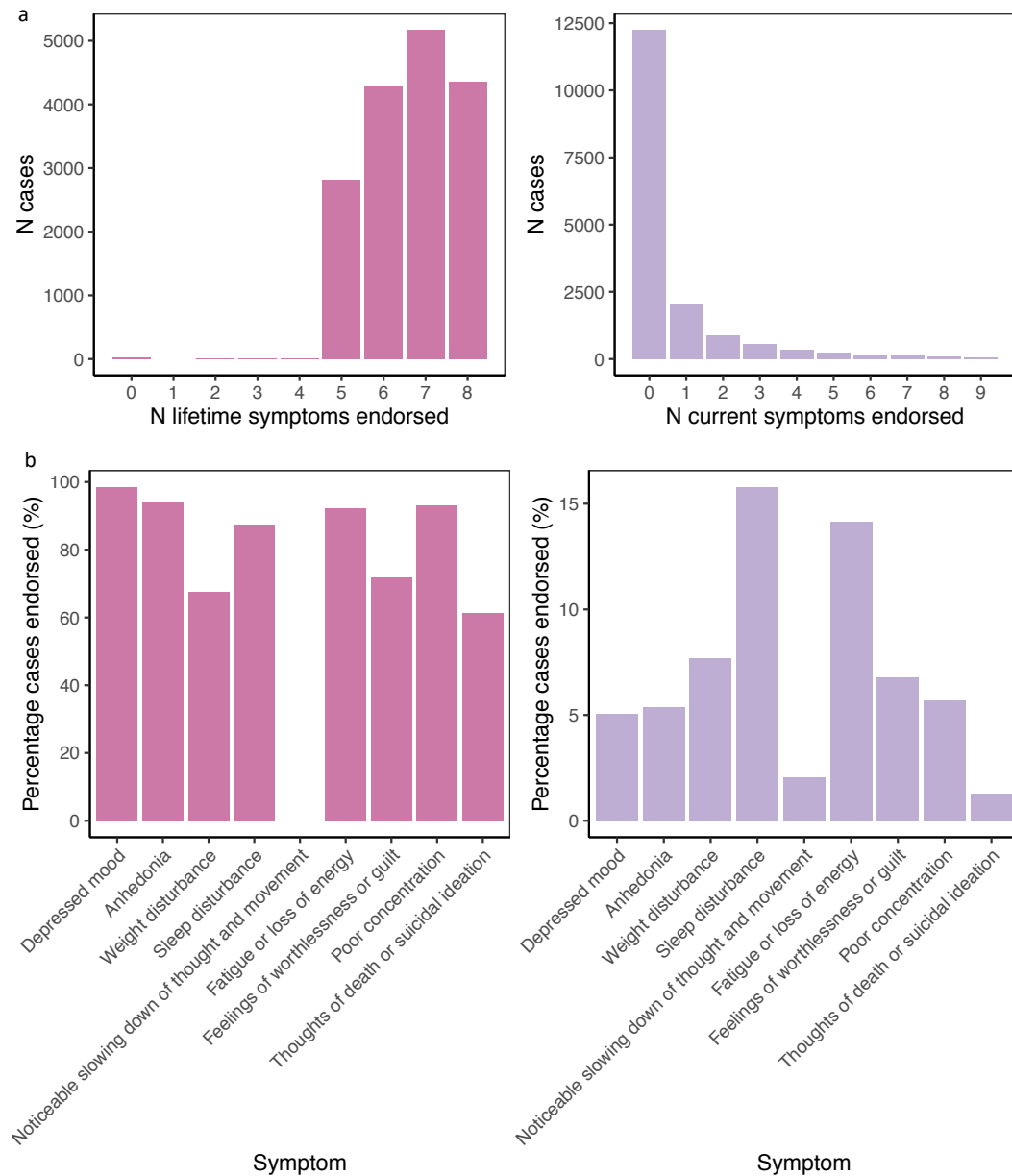
Supplementary Figure 1: Symptoms of CIDI-based MDD LifetimeMDD in UKBiobank

a) This Figure hows the number of DSM-V criterion A symptoms endorsed by cases of LifetimeMDD defined in Supplementary Methods: the panel on the left (darker purple) shows the number of lifetime symptoms given in answer to the mental health questionnaire (MHQ); the panel on the right (lighter purple) shows the number of symptoms experienced over the two weeks leading up to the Touchscreen questionnaire. Those endorsing 0-4 lifetime symptoms in the left panel would have been classified as cases of LifetimeMDD because they endorsed 5 or more current symptoms in the right panel, including either "Depressed mood" or "Anhedonia". b) This Figure hows the percentage of cases of LifetimeMDD endorsing each of the DSM-V criterion A symptoms: the panel on the left (darker purple) shows the endorsement for each symptom in one's life up to point of assessment; the panel on the right (lighter purple) shows the endorsement for having each symptom over the two weeks leading up to the Touchscreen questionnaire.
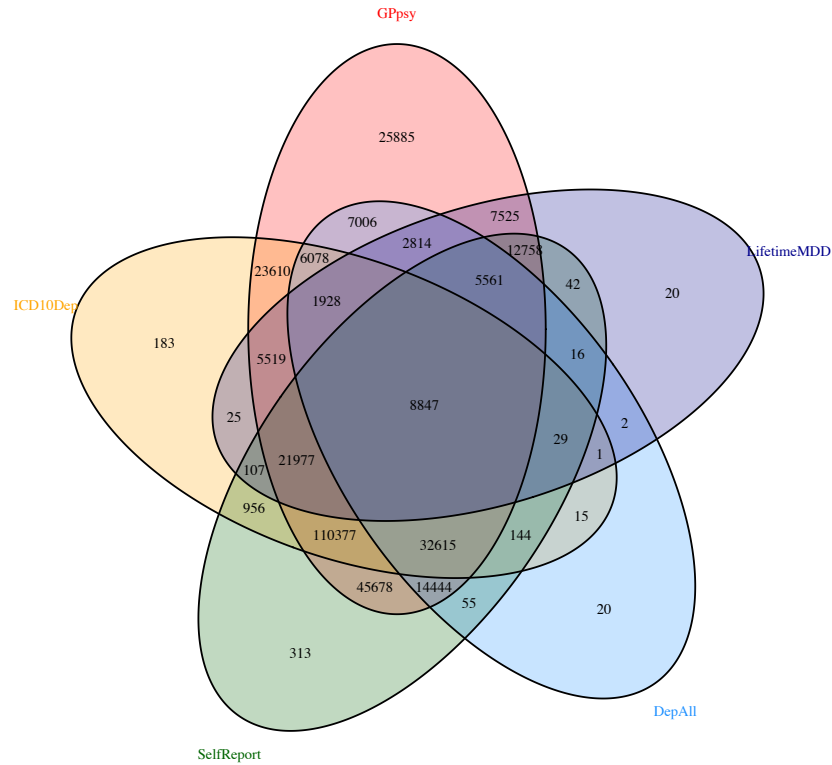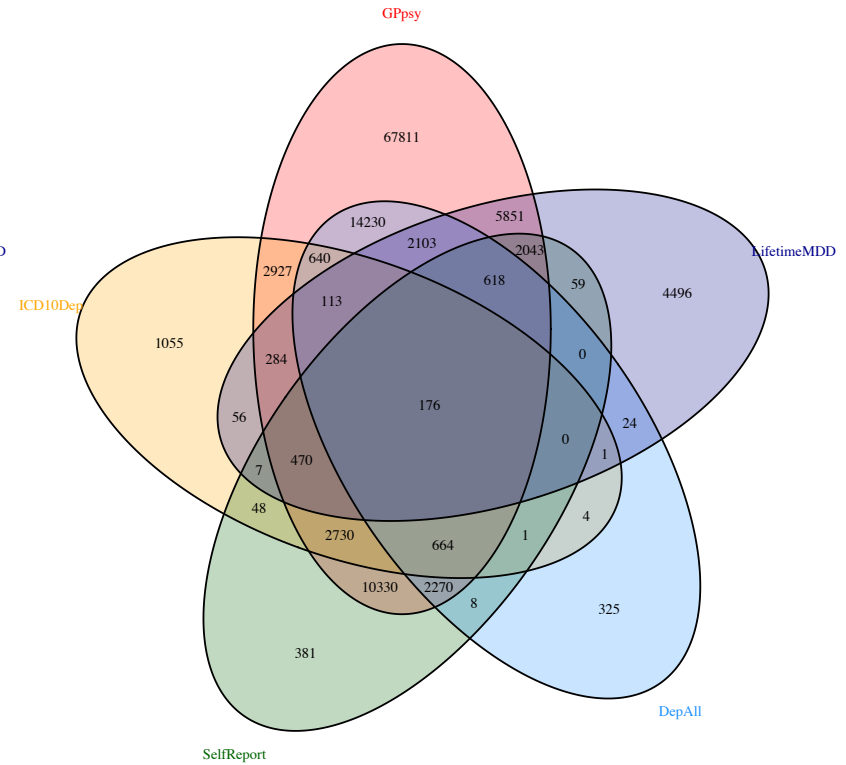
Supplementary Figure 2: Overlap between definitions of MDD in UKBiobank

a) This Figure hows the number of overlapping cases between help-seeking (GPpsy in red), symptom (DepAll, in blue), self-report (SelfRepDep, in green), CIDI (LifetimeMDD, in purple) based definitions of MDD, as well as the electronic health record (EMR) based, ICD10 code derived depression (ICD10Dep, in orange). As not all individuals answered all questions necessary to assess whether they are a case or control in any of the definitions of MDD, we also show in b) the number of overlapping individuals (both cases and controls) who answered the question necessary to qualify as either cases or controls in each of the definitions of MDD (refer to main text and Figure 1 for details).
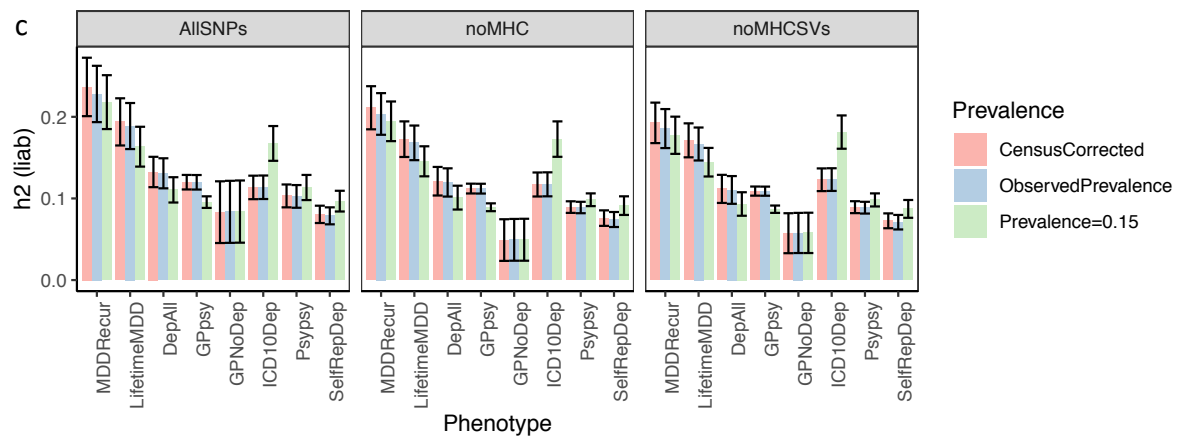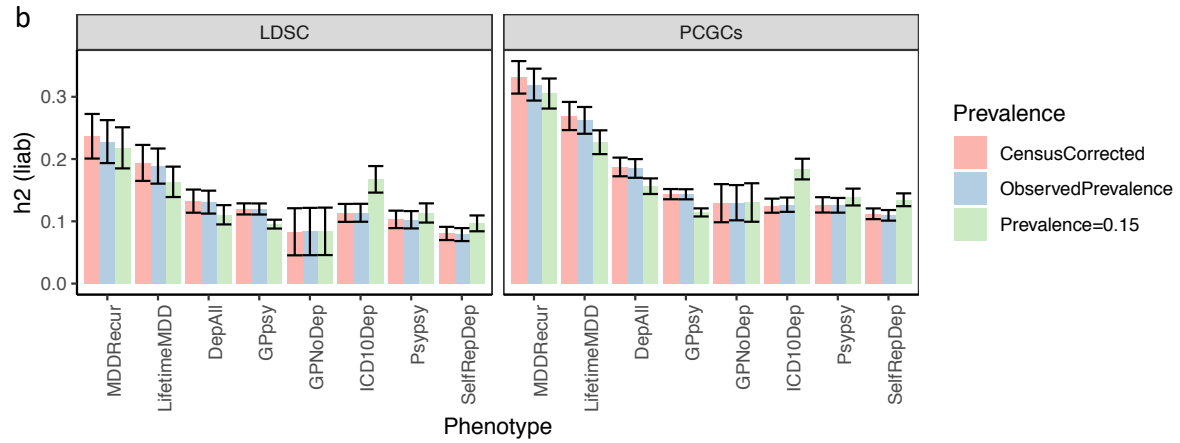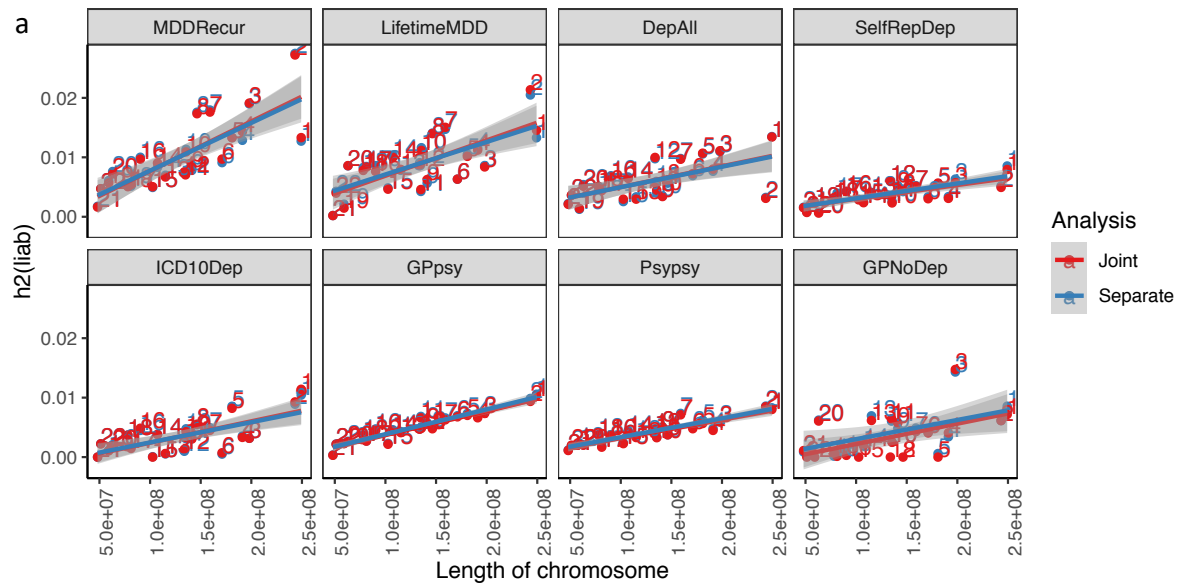
Supplementary Figure 3: Effects of population structure and MHC/SVs

a) This Figure hows for each definition of depression in UKBiobank the estimates of h^2_{SNP} (on the liability scale) contributed by each chromosome (obtained using BOLT-REML, see Supplementary Methods) estimated both jointly (in red) and separately (in blue), plotted against the lengths of the chromosomes, using both PCs obtained from the whole White-British cohort in UKBiobank. Error bars show the standard errors of the estimates. Shaded area represent 95% confidence interval of the regression line. b) This Figure hows for each definition of depression in UKBiobank estimtates of h^2_{SNP} (on the liability scale) from PCGCs and LDSC: for each method, we obtained estimates using as population prevalence the observed prevalence (light blue), census corrected prevalence (light red) and assumed prevalence of 0.15 as per PGC1-MDD (light green). Error bars show the standard errors of the estimates. c) This Figure hows for each definition of depression in UKBiobank the h^2_{SNP} estimates from LDSC using all SNPs > 5% MAF (LDSC-AllSNPs), all SNPs > 5% MAF except those in the MHC region on chromosome 6:25-35MB (LDSC-noMHC), and all SNPs > 5% MAF except those in the MHC region and SVs[9]. The colour scheme reflects the population prevalence used in the analysis as explained in b). Error bars show the standard errors of the estimates.
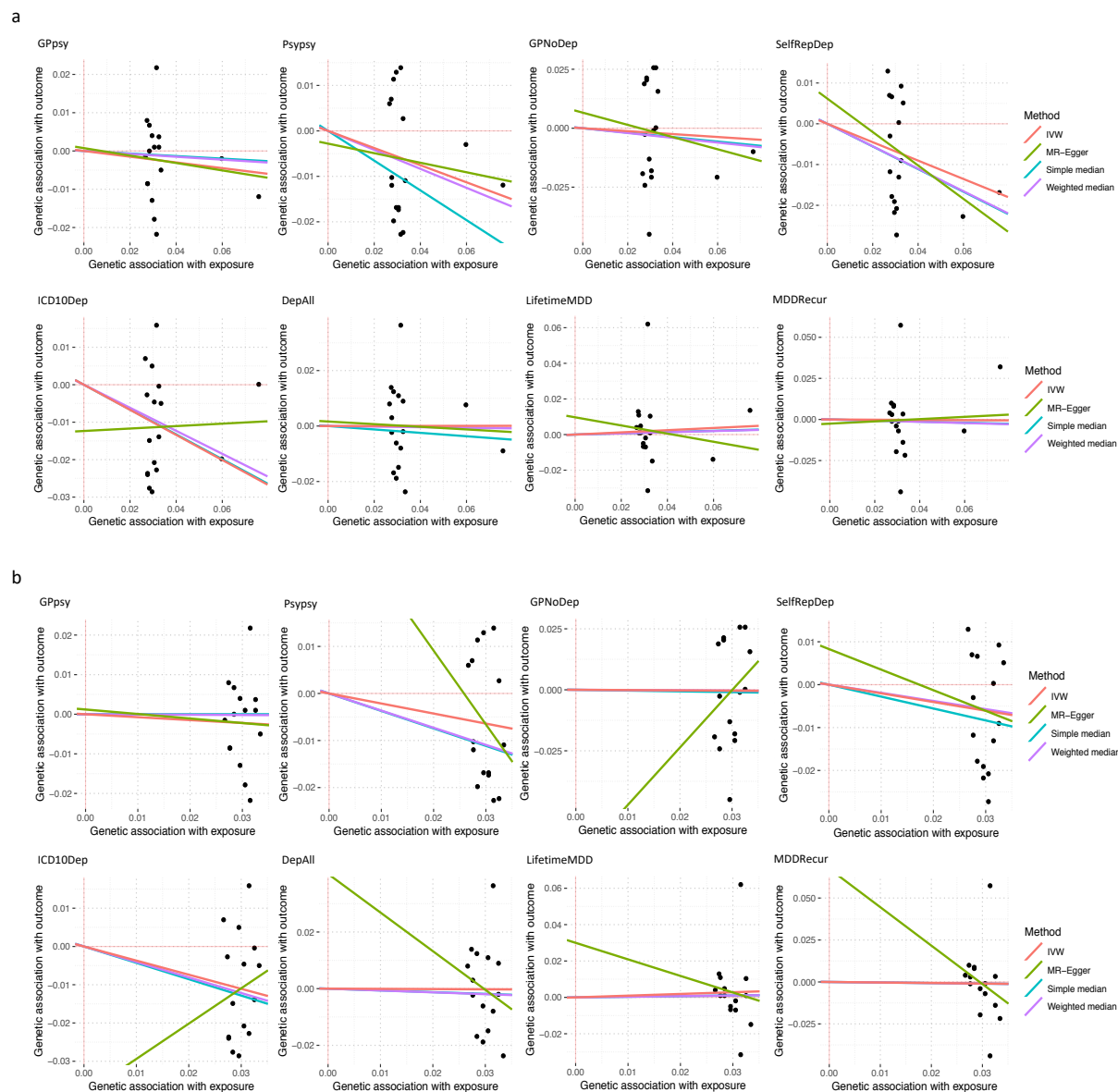
Supplementary Figure 4: Effect of MHQ participation on definitions of depression
a) This Figure hows the results from Mendelian Randomization (MR) assessment of SNPs significantly associated with MHQ participation for their effects on definitions of depression in UKBiobank, using the following estimators: inverse variance weighted (IVW), MR-Egger, Simple median, and Weighted median. None of the estimators show significant causal effect between MHQ participation on definitions of depression (Supplementary Table 9). b) This Figure hows the same results, removing two SNPs rs429358 and rs1261078 which have large effects on MHQ participation. Again no estimators show significant causal effects between MHQ participation on definitions of depression.
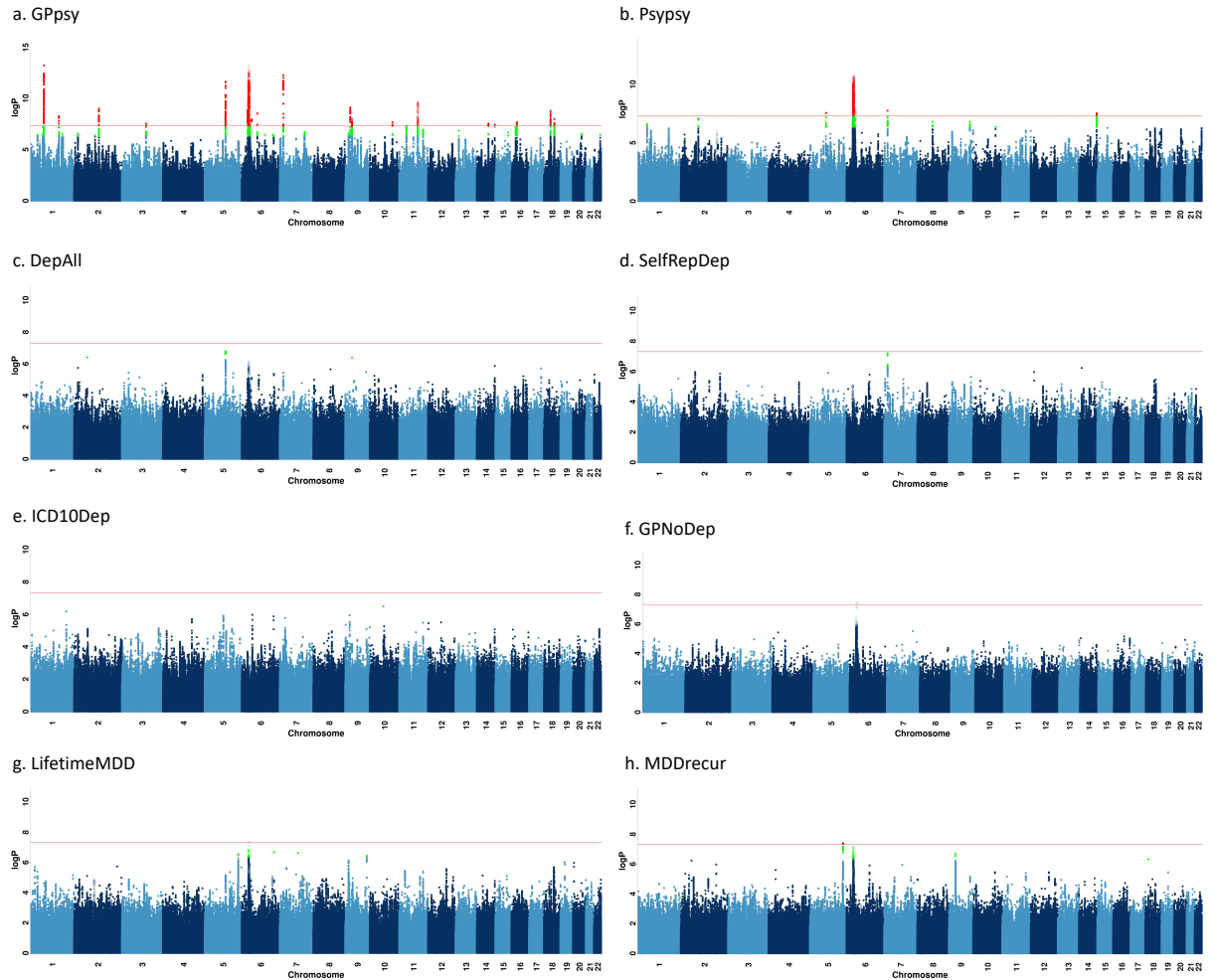
Supplementary Figure 5: GWAS on definitions of depression using "clean" controls

a-h) These figures shows Manhattan plots of GWAS on each definition of depression performed with logistic regression as described in Methods, using "clean" controls rather than all controls. We report all associations with P-values smaller than 5×10^{-8} as genome-wide significant (red). We indicated the SNPs in SVs and the MHC in all Manhattan plots as hollow points instead of solid points due to lack of control for population structure in these regions, and show all top SNPs within peaks (1MB regions) in Supplementary Table 11.
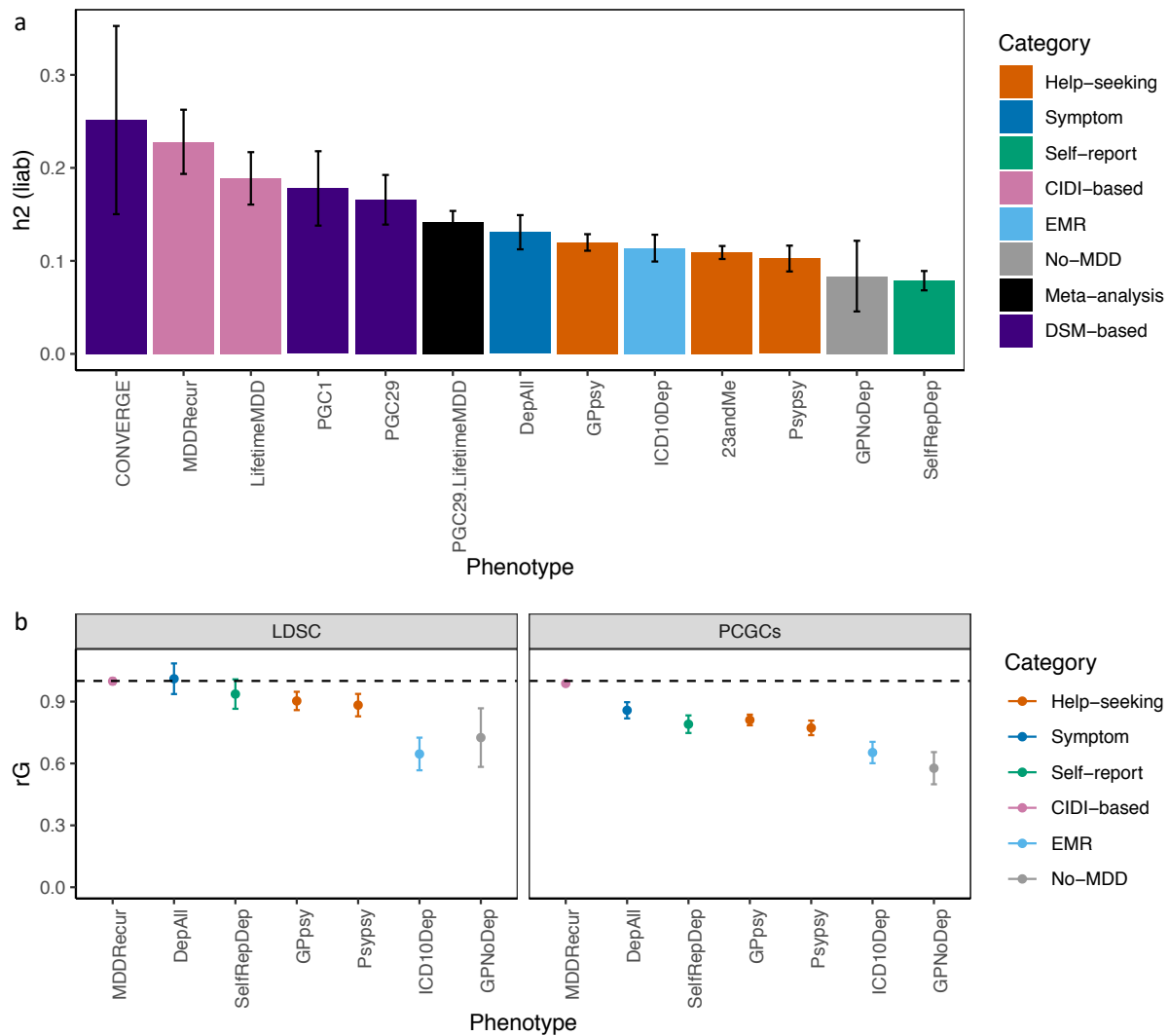
Supplementary Figure 6: LDSC estimates of heritability and genetic correlation

a) This Figure hows the h^2_{SNP} estimates of definitions of MDD in UKBiobank from LDSC using logistic regression summary statistics on all SNPs > 5% MAF (Methods). Error bars show the standard errors of the estimates. In the figure we also show LDSC estimates of heritabilities of previous studies of MDD including CONVERGE[26], PGC1-MDD[8], PGC29-MDD, a meta-analysis between CIDI-based LifetimeMDD and PGC29-MDD excluding individuals in UKBiobank (PGC29.LifetimeMDD), and 23andMe[27]. We show CIDI-based definitions in UKBiobank (in purple) show similar estimates to CONVERGE, symptom-based definitions in UKBiobank (in blue) are similar to PGC1-MDD, while help-seeking based (in red) definitions in UKBiobank are similar to 23andMe. b) This Figure hows the genetic correlation between all definitions of MDD in UKBiobank against a CIDI-based definition of MDD (LifetimeMDD) estimated in LDSC and PCGCs (duplicated from Figure 3b for comparison). Error bars show the standard errors of the estimates.
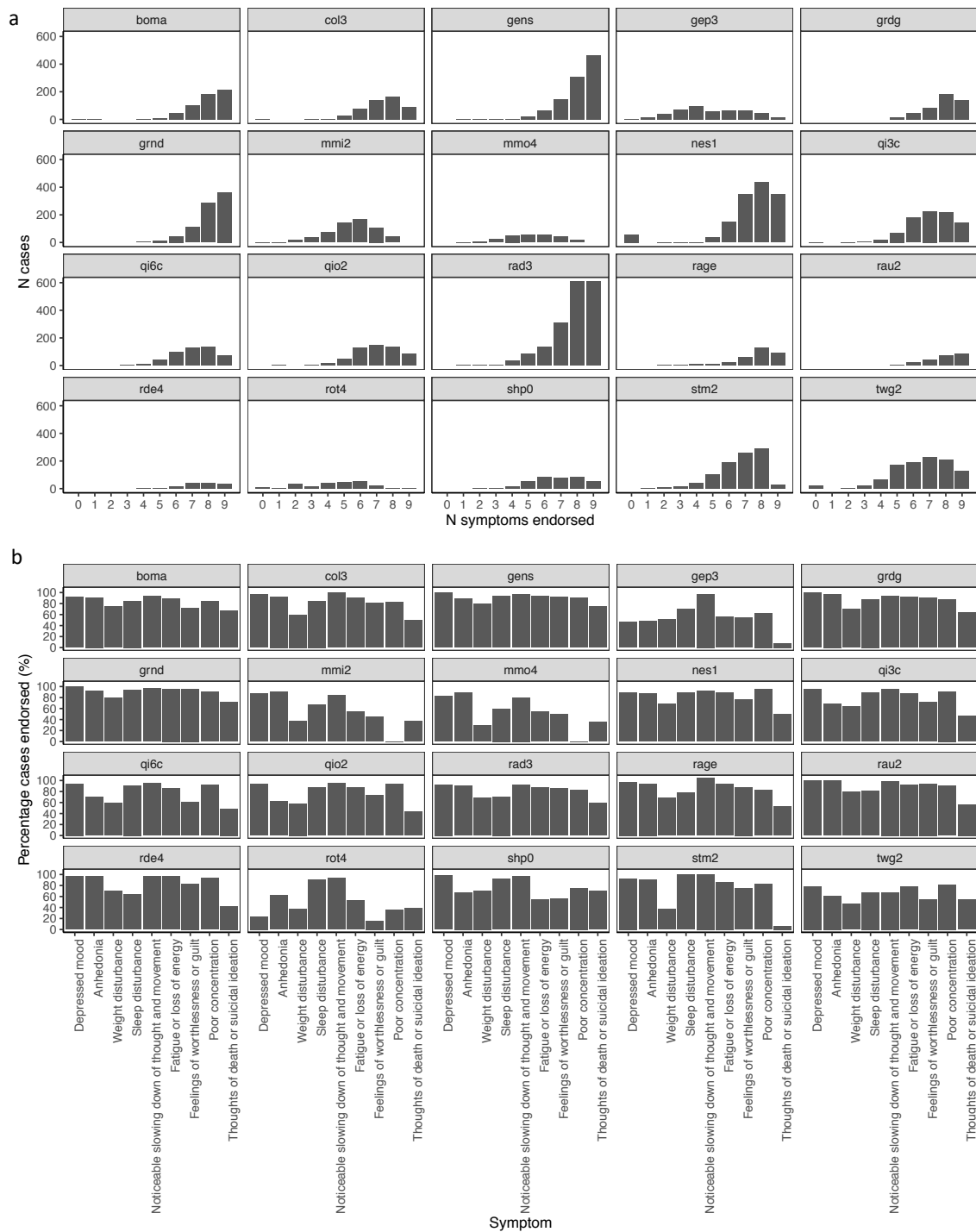
Supplementary Figure 7: Symptoms of MDD cases in PGC cohorts

a) The number of DSM-5 criterion A symptoms, defined as described in Supplementary Methods, endorsed by cases of MDD in 23 PGC cohorts. Those endorsing 0-4 lifetime symptoms, or more symptoms without endorsing "Depressed mood" or "Anhedonia", would not be included in the "DSM-MDD" cases we define in each PGC cohort, as shown in Supplementary Table 21. b) The percentage of cases of MDD in PGC cohorts endorsing each of the DSM-5 criterion A symptoms.

Supplementary Tables

ABBREVIATION	PHENOTYPE	COLLECTION STRATEGY	STUDY TYPE	REFERENCE	N	SAMPLE PREV	POPULATION PREV	PREVALENCE REFERENCE
CONVERGE	MDD	Hospital based psychiatrist diagnosis	case-ascertained, screened-controls	CONVERGE Consortium, 2015	10640	0.50	0.08	CONVERGE Consortium, 2015
PGC1-MDD	MDD	Structured telephone interviews	case-ascertained, screened-controls (mega-analysis)	MDD Working Group of the Psychiatric Genomics Consortium, 2013	18759	0.50	0.15	Kessler et al., 2003
PGC29	MDD	Structured telephone interviews/electronic health records	case-ascertained, some screened-controls (meta-analysis)	MDD Working Group of the Psychiatric Genomics Consortium, 2018	42455	0.40	0.15	Kessler et al., 2003
23andMe	MDD	Minimal phenotyping: self-report via single question in questionnaire	unascertained population cohort	Hyde et al., 2016	307354	0.25	0.25	Hyde et al., 2016
ADHD	ADHD	Hospital based psychiatrist diagnosis	case-ascertained, screened-controls (mega-analysis)	Demontis et al., 2017	53293	0.36	0.05	Demontis et al., 2017

BIP	BIP	Hospital based psychiatrist diagnosis	case-ascertained, 33% screened-controls (mega-analysis)	Bipolar Disorder Working Group of the Psychiatric Genomics Consortium, 2011	16731	0.45	0.025	Merikangas et al., 2011
SCZ	SCZ	Hospital based psychiatrist diagnosis /semi-structured interviews	case-ascertained, population-controls; trios (mega-analysis)	Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014	150064	0.25	0.01	Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014
AUT	AUT	Hospital based psychiatrist diagnosis	trios; case-ascertained, population-controls (mega-analysis)	Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013	10610	0.50	9×10^{-4}	Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013

Supplementary Table 1: Other studies referenced in this paper
This Table shows the studies from which we obtain GWAS summary statistics for MDD and other psychiatric conditions that we reference in this paper. The columns are abbreviations of the studies used in this paper, the disease phenotype in question, their case collection strategy, their study type where known, the study reference, number of samples involved, case prevalence in sample, population prevalence of disease phenotypes, and reference for population prevalence of disease prevalence if different from the reference of the study itself.

DSM CRITERIA	DATA FIELD	QUESTION ON LIFETIME MDD	QUALIFYING ANSWERS	N_YES	N_NO
A1	20446	Have you ever had a time in your life when you felt sad, blue, or depressed for two weeks or more in a row?	Yes	59409	50018
A2	20441	Have you ever had a time in your life lasting two weeks or more when you lost interest in most things like hobbies, work, or activities that usually give you pleasure?	Yes	42565	66830
A3	20536	Did you gain or lose weight without trying, or did you stay about the same weight?	Gained weight, Lost weight, Both gained and lost some weight during the episode	30875	21324
A4	20532	Did your sleep change?	Yes	41955	10714
A6	20449	Did you feel more tired out or low on energy than is usual for you?	Yes	45034	10072
A7	20450	People sometimes feel down on themselves, no good, worthless. Did you feel this way?	Yes	28865	28472
A8	20435	Did you have a lot more trouble concentrating than usual?	Yes	42568	11592
A9	20437	Did you think a lot about death - either your own, someone else's or death in general?	Yes	29946	27856
DSM CRITERIA	DATA FIELD	QUESTION ON CURRENT MDD: Over the last 2 weeks, how often have you been bothered by any of the following problems?	QUALIFYING ANSWERS	N_YES	N_NO
A1	20510	Feeling down, depressed, or hopeless	Nearly every day	1449	108261

A2	20514	Little interest or pleasure in doing things	Nearly every day	1670	108040
A3	20511	Poor appetite or overeating	Nearly every day	2633	107077
A4	20517	Trouble falling or staying asleep, or sleeping too much	Nearly every day	8616	101094
A5	20518	Moving or speaking so slowly that other people could have noticed? Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual	Nearly every day	650	109060
A6	20519	Feeling tired or having little energy	Nearly every day	5968	103742
A7	20507	Feeling bad about yourself or that you are a failure or have let yourself or your family down	Nearly every day	2166	107544
A8	20508	Trouble concentrating on things, such as reading the newspaper or watching television	Nearly every day	1769	107941
A9	20513	Thoughts that you would be better off dead or of hurting yourself in some way	Nearly every day	357	109353

Supplementary Table 2: CIDI-based criteria for lifetime and current MDD

This table lists questions in the online mental health follow up questionnaire in UKBiobank forming the DSM-V diagnostic criteria for lifetime MDD[5] (Question on lifetime MDD) and current MDD (Question on current MDD), along with their data field in UKBiobank data showcase (datafield), the DSM criteria they correspond to, and the multiple-choice answer to each of the questions which indicates a subject as self-reporting having the symptom.

Other criteria		GPNoDep		
		Controls	Cases	Total
MHQ	Answered MHQ	13514	1541 (10.2%)	15055
	Did not answer MHQ	35979	7091 (16.5%)	43070
Self-report	Self-reported illness	36474	7139 (16.4%)	43613
	Did not self-report illness	13019	1439 (10.0%)	14458

Supplementary Table 3: Characterizing no-MDD definition GPNoDep

This Table shows the number of cases and controls in the no-MDD definition GPNoDep that answered or did not answer either the mental health questionnaire (MHQ) in the online mental health follow-up, or self-reported any illness in the verbal interview. The proportion of GPNoDep cases who answered the self-reported non-cancer illnesses during the verbal interview (16.4%) is significantly different from the proportion who did not answer (10.0%, Chisq test $P < 10^{-16}$, df = 1). Similarly, the proportion of GPNoDep cases who asnwered the MHQ (10.2%) is significantly different from the proportion who did not (16.5%, Chisq test $P < 10^{-16}$, df = 1).

CENTRE	DEFINITION OF DEPRESSION (N_CASES/N_CONTROLS)							
	CIDI-BASED		SYMPTOM	SELF-REPORT	HELP-SEEKING		NO-MDD	EMR
	LifetimeMDD	MDDRecur	DepAll	SelfRepDep	GPpsy	Psypsy	GPNoDep	ICD10Dep
Barts	399/1075	274/1040	NA	292/3623	1941/3795	1025/4728	NA	146/3154
Birmingham	869/2333	563/2239	3198/7995	816/10902	5536/10139	1922/13782	1186/6769	450/9247
Bristol	1613/5047	1001/4880	1649/4643	1534/21046	9817/20411	2960/27335	655/3972	738/18452
Bury	826/2436	512/2347	NA	1506/15186	6971/13005	2118/17939	NA	708/13533
Cardiff	554/1660	361/1599	NA	603/8663	4357/8239	1345/11285	NA	364/8022
Croydon	801/2937	500/2842	2744/7922	811/10644	4706/9985	1791/12915	1074/6821	360/8331
Edinburgh	568/2092	336/2033	NA	551/7368	3851/8325	1305/10889	NA	106/5784
Glasgow	480/1605	309/1565	NA	771/8505	4550/7961	1553/10998	NA	158/7406
Hounslow	743/3060	472/2954	2489/7862	619/9990	4401/9948	1741/12642	1055/6775	309/7978
Leeds	1503/4312	932/4146	NA	2058/20840	10701/20079	3379/27457	NA	805/18691
Liverpool	1080/3024	700/2916	2651/7765	1609/16421	7792/14444	2377/19930	1221/6500	875/14622
Manchester	469/1282	321/1218	NA	821/6855	3244/5654	1091/7818	NA	304/5961
Middlesborough	788/2175	504/2093	2934/8017	826/10477	5319/9595	1447/13520	1239/6727	650/9660
Newcastle	1165/3363	746/3246	NA	1355/18166	9120/16690	2836/23035	NA	908/17522
Nottingham	1208/3541	744/3420	676/1929	1325/17305	8178/15766	2515/21492	281/1639	636/15239
Oxford	455/1695	274/1639	NA	656/6793	3236/6577	1148/8690	NA	205/5427
Reading	999/4126	614/3995	NA	947/13561	6298/14662	1950/19033	NA	379/11477
Sheffield	1125/3218	731/3081	4370/11248	1664/16219	7656/13696	2070/19329	1763/9436	581/12965
Stockport_pilot	45/90	27/87	NA	33/247	108/207	30/287	NA	10/196
Stoke	485/1519	299/1474	NA	874/9823	4700/8913	1443/12210	NA	424/8216
Swansea	93/228	59/221	360/762	107/1147	609/964	188/1385	127/632	39/1048
Wrexham	33/52	23/48	106/255	27/333	169/307	52/427	31/222	21/304

Supplementary Table 4: Number of samples by assessment centre

This table lists the number of cases (N_cases) and controls (N_controls) collected for each of the definitions in UKBiobank in the categories CIDI-based, Symptom, Self-report, Help-seeking, and no-MDD collected in each assessment centre. "NA" denotes no collection of answers to questions that form diagnostic criteria to the relevant definition of MDD in an assessment centre.

CATEGORY	DEFINITION	NSAMPLES	PREV	CORRECTED_PREV
CIDI-based	LifetimeMDD	67171	0.243	0.268
CIDI-based	MDDRecur	59385	0.173	0.196
Symptom	DepAll	79576	0.266	0.279
Self-report	SelfRepDep	253926	0.078	0.084
EMR	ICD10Dep	212411	0.043	0.043
Help-seeking	GPpsy	332629	0.341	0.343
Help-seeking	Psypsy	333419	0.109	0.111

Supplementary Table 5: Prevalence of each definition of MDD
This Table shows for each definition of MDD in UKBiobank the category we assign it to (CIDI-based, Symptom, Self-report, Help-seeking, or no-MDD), the number of samples (both cases and controls), the case prevalence (prev), and the case prevalence when corrected for age group, sex and population in each assessment centre where samples are collected. Correction factors for age, sex and population in each assessment centre are shown in Supplementary Tables 5,6.

| CENTRE | UKBIOBANK | | CENSUS_2011 | | CORRECTION |
	N_SAMPLE	FRACTION	POPULATION	POP_FRACTION	
Cardiff	12678	0.038	346090	0.044	1.151
Sheffield	21479	0.064	552698	0.070	1.085
Hounslow	14439	0.043	253957	0.032	0.742
Leeds	30964	0.093	751485	0.095	1.023
Croydon	14778	0.044	363378	0.046	1.037
Birmingham	15783	0.047	1073045	0.135	2.866
Bristol	30406	0.091	428234	0.054	0.594
Nottingham	24106	0.072	305680	0.039	0.535
Reading	21050	0.063	155698	0.020	0.312
Liverpool	22399	0.067	466415	0.059	0.878
Newcastle	25963	0.078	280177	0.035	0.455
Stoke	13705	0.041	249008	0.031	0.766
Middlesborough	15024	0.045	138412	0.017	0.388
Manchester	8949	0.027	503127	0.063	2.370
Bury	20138	0.060	185060	0.023	0.387
Glasgow	12589	0.038	593245	0.075	1.987
Oxford	9865	0.029	151906	0.019	0.649
Edinburgh	12224	0.037	476626	0.060	1.644
Barts	5779	0.017	7375	0.001	0.054
Wrexham	481	0.001	134844	0.017	11.819
Stockport_pilot	317	0.001	283275	0.036	37.675
Swansea	1583	0.005	239023	0.030	6.366

Supplementary Table 6: Correction for population in assessment centres

This table shows the number of samples (N_sample) and the fraction of total sample size (fraction) from each assessment centre in UKBiobank, as well as the population in cities where each of the collection centres are located (population) and the fraction of the UK population they represent (pop_fraction) according to the UK Census 2011. Only cities where there are UKBiobank assessment centres are included in this table and considered when calculating fractions of the UK population. The correction factor (correction) is the ratio between the population fraction and sample fraction, and is multiplied to the case prevalence of each definition of MDD from each assessment centre when calculating the corrected prevalence for each definition of MDD across all assessment centres, along with correction factors for age and sex as shown in Supplementary Table 7.

AGE	UKBIOBANK			CENSUS_2011		CORRECTION	
	N_SAMPLE	% AGE	% FEMALE	% AGE	% FEMALE	AGE	FEMALE
39to44	31412	9.4	53.3	17.6	50.1	1.875	0.940
45to49	41684	12.5	55.3	17.7	50.3	1.421	0.909
50to54	49730	14.9	56.3	15.6	50.6	1.050	0.898
55to59	60517	18.1	55.4	13.8	50.6	0.763	0.913
60to64	84850	25.4	53.7	14.5	50.4	0.572	0.938
above65	66506	19.9	49.6	26.0	50.8	1.308	1.023

Supplementary Table 7: Correction for age and sex

This Table shows the number of samples (N_sample) and the fraction of total sample size of each age group (% age) as well as fraction of females (% female) per age group in UKBiobank, as well as the fraction of the UK population from each age group (% age) and who are female (% female) per age group according to the UK Census 2011. Only age groups of those ages of samples included in UKBiobank are shown in this table and considered when calculating fractions of each age group and sex. Correction factors (age, sex) are the ratios between the population fraction and sample fraction of each age group and sex, and are multiplied by the case prevalence of each definition of MDD along with correction factors for assessment centre population as shown in Supplementary Table 6 when calculating the corrected prevalence for each definition of MDD.

CHR	RSID	BP	A1	A0	A1FREQ	OR	SE	P	USED IN MR	REASON NOT USED
1	rs7542974	72,544,704	A	G	0.25	1.032	0.0053	3.80E-08	YES	
1	rs485929	74,678,285	G	A	0.39	1.028	0.0048	3.70E-08	YES	
1	rs532246	84,411,238	G	A	0.74	0.968	0.0051	7.00E-09	YES	
1	rs2789111	243,346,404	C	T	0.38	0.968	0.0054	1.50E-10	NO	INFO < 0.9
2	rs35028061	49,479,987	GT	G	0.38	1.029	0.005	1.90E-08	NO	INDEL
3	rs9917656	48,581,513	C	T	0.3	1.03	0.0056	3.20E-08	YES	
3	rs13082026	52,962,681	T	C	0.44	0.972	0.005	2.40E-08	NO	INFO < 0.9
4	rs57692580	106,214,476	A	T	0.39	0.973	0.0046	2.80E-08	NO	INFO < 0.9
5	rs34635	60,513,501	G	A	0.42	0.972	0.0045	1.20E-08	NO	INFO < 0.9
5	rs146681214	133,867,867	AC	A	0.18	1.039	0.0065	3.60E-09	NO	INDEL
5	rs2336897	167,050,276	T	C	0.69	1.031	0.0061	5.20E-09	YES	
6	rs3993747	31,580,507	G	A	0.35	0.969	0.0044	9.50E-10	YES	
6	rs59732267	98,432,302	CA	C	0.52	0.972	0.0047	2.50E-08	NO	INDEL
8	rs28716319	83,269,854	G	A	0.28	1.031	0.0057	2.70E-08	YES	
8	rs13262595	143,316,970	G	A	0.56	1.03	0.005	1.00E-09	YES	
9	rs6474966	15,757,537	A	G	0.46	1.028	0.0049	2.80E-08	YES	
9	rs11793831	23,362,311	T	G	0.42	1.027	0.0053	4.30E-08	YES	
11	rs1984389	31,740,989	C	A	0.54	0.973	0.0046	2.40E-08	YES	
11	rs10791143	131,278,676	G	A	0.62	1.034	0.0046	1.50E-11	YES	
16	rs4616299	7,657,432	G	A	0.4	0.972	0.005	1.20E-08	YES	
17	rs56058331	56,427,128	A	G	0.42	1.029	0.0047	1.00E-08	NO	INFO < 0.9
18	rs1261078	52,866,791	G	A	0.05	0.927	0.0107	5.60E-12	YES	
19	rs34232444	4,965,404	C	T	0.35	1.029	0.0057	2.50E-08	NO	INFO < 0.9
19	rs3746187	18,279,816	G	A	0.4	0.968	0.0049	9.80E-11	YES	
19	rs429358	45,411,941	C	T	0.15	0.942	0.0067	4.60E-19	YES	

Supplementary Table 8: GWAS hits for participation in the MHQ (adapted from Adams et al 2019)

This Table shows the genome-wide significant loci (top SNP in 1MB regions) in GWAS for participation in the MHQ, as reported in Adams et al 2019 [6]. For each locus, we show the chromosome (CHR), rsid for independent significant variants (RSID), position on the chromosome (BP), test allele (A1), other allele (A0), allele frequency of the test allele (A1FREQ) in all White-British samples in UKBiobank, odds ratio of the test allele on the phenotype (OR), standard error of the OR (SE), p-value of the association from logistic regression (P), and whether the locus is used in the Mendelian Randomisation analysis with definitions of depression in UKBiobank (USED IN MR), and reason if it is not used (REASON NOT USED).

CATEGORY	DEFINITION	METHOD	All 16 MHQ GWAS SNPs				REMOVE 2 OUTLIERS			
			ESTIMATE	SE	95% CI	P	ESTIMATE	SE	95% CI	P
CIDI-based	LifetimeMDD	Simple Median	0.035	0.147	[-0.252,0.323]	0.810	0.035	0.165	[-0.288,0.359]	0.831
		Weighted Median	0.033	0.141	[-0.244,0.310]	0.816	0.035	0.162	[-0.282,0.351]	0.829
		IVW	0.062	0.144	[-0.220,0.343]	0.668	0.094	0.168	[-0.234,0.423]	0.574
		MR-Egger	-0.229	0.606	[-1.417,0.960]	0.706	-0.910	2.464	[-5.739,3.919]	0.712
		MR-Egger intercept	0.010	0.020	[-0.029,0.048]	0.622	0.030	0.073	[-0.114,0.174]	0.683
	MDDRecur	Simple Median	-0.033	0.175	[-0.376,0.310]	0.851	-0.033	0.196	[-0.417,0.352]	0.867
		Weighted Median	-0.036	0.172	[-0.373,0.300]	0.833	-0.033	0.193	[-0.411,0.345]	0.864
		IVW	-0.007	0.156	[-0.313,0.298]	0.963	-0.032	0.182	[-0.389,0.326]	0.862
		MR-Egger	0.069	0.658	[-1.220,1.358]	0.917	-2.290	2.624	[-7.432,2.853]	0.383
		MR-Egger intercept	-0.003	0.021	[-0.044,0.039]	0.905	0.067	0.078	[-0.086,0.221]	0.388
Symptom	DepAll	Simple Median	-0.061	0.136	[-0.327,0.205]	0.651	-0.061	0.157	[-0.369,0.246]	0.695
		Weighted Median	-0.010	0.132	[-0.269,0.248]	0.937	-0.065	0.152	[-0.363,0.234]	0.672
		IVW	0.001	0.113	[-0.220,0.222]	0.993	-0.008	0.134	[-0.270,0.255]	0.954
		MR-Egger	-0.048	0.471	[-0.971,0.875]	0.919	-1.363	1.947	[-5.180,2.454]	0.484
		MR-Egger intercept	0.002	0.015	[-0.028,0.032]	0.915	0.041	0.058	[-0.073,0.154]	0.485
Self-report	SelfRepDep	Simple Median	-0.278	0.127	[-0.527,-0.029]	0.028	-0.278	0.150	[-0.573,0.017]	0.065
		Weighted Median	-0.276	0.124	[-0.519,-0.033]	0.026	-0.190	0.142	[-0.468,0.088]	0.180
		IVW	-0.226	0.096	[-0.414,-0.037]	0.019	-0.202	0.114	[-0.425,0.021]	0.075
		MR-Egger	-0.410	0.401	[-1.196, 0.376]	0.307	-0.480	1.665	[-3.743,2.783]	0.773
		MR-Egger intercept	0.006	0.013	[-0.019, 0.032]	0.636	0.008	0.050	[-0.089,0.106]	0.867
EMR	ICD10Dep	Simple Median	-0.331	0.169	[-0.662,-0.001]	0.050	-0.427	0.190	[-0.800,-0.055]	0.025
		Weighted Median	-0.307	0.166	[-0.633, 0.018]	0.064	-0.405	0.187	[-0.771,-0.039]	0.030
		IVW	-0.335	0.120	[-0.571,-0.099]	0.005	-0.369	0.135	[-0.633,-0.105]	0.006
		MR-Egger	0.033	0.485	[-0.919, 0.984]	0.947	0.922	1.916	[-2.832,4.677]	0.630
		MR-Egger intercept	-0.012	0.016	[-0.043, 0.019]	0.434	-0.039	0.057	[-0.151,0.073]	0.499
Help-seeking	GPpsy	Simple Median	-0.033	0.067	[-0.165,0.098]	0.619	0.000	0.081	[-0.159,0.159]	1.000

		Weighted Median	-0.038	0.065	[-0.166,0.090]	0.563	-0.006	0.078	[-0.159,0.147]	0.936
		IVW	-0.075	0.078	[-0.227,0.078]	0.336	-0.074	0.093	[-0.255,0.108]	0.426
		MR-Egger	-0.097	0.327	[-0.738,0.544]	0.766	-0.114	1.368	[-2.796,2.568]	0.934
		MR-Egger intercept	0.001	0.011	[-0.020,0.022]	0.944	0.001	0.041	[-0.079,0.081]	0.977
	Psypsy	Simple Median	-0.327	0.108	[-0.539,-0.115]	0.003	-0.371	0.126	[-0.618,-0.124]	0.003
		Weighted Median	-0.209	0.102	[-0.409,-0.008]	0.042	-0.364	0.122	[-0.604,-0.125]	0.003
		IVW	-0.189	0.098	[-0.380, 0.003]	0.053	-0.213	0.116	[-0.440,0.013]	0.065
		MR-Egger	-0.105	0.408	[-0.904, 0.694]	0.797	-1.568	1.665	[-4.832,1.696]	0.346
		MR-Egger intercept	-0.003	0.013	[-0.029, 0.023]	0.833	0.040	0.050	[-0.057,0.138]	0.415
Non-MDD	GPNoDep	Simple Median	-0.094	0.200	[-0.487,0.299]	0.638	-0.032	0.233	[-0.489,0.425]	0.892
		Weighted Median	-0.102	0.195	[-0.483,0.280]	0.602	-0.012	0.221	[-0.446,0.422]	0.958
		IVW	-0.062	0.160	[-0.376,0.252]	0.698	-0.012	0.188	[-0.381,0.358]	0.951
		MR-Egger	-0.259	0.670	[-1.572,1.054]	0.699	2.350	2.695	[-2.932,7.632]	0.383
		MR-Egger intercept	0.007	0.022	[-0.036,0.049]	0.762	-0.071	0.080	[-0.228,0.087]	0.380

Supplementary Table 9: Assessing casual relationship between MHQ participation and definitions of depression

This Table shows the results from Mendelian Randomization (MR) assessment of SNPs significantly associated with MHQ participation for their effects on definitions of depression in UKBiobank, using the following estimators: inverse variance weighted (IVW), MR-Egger, Simple median, and Weighted median. The analysis is performed using both all 16 MHQ associated SNPs as shown in Supplementary Table 8, or removing two SNPs rs429358 and rs1261078 which have large effects on MHQ participation.

CATEGORY	PHENO	NSAMPLES	CHR	SNP	BP	A1	A0	A1FREQ	OR	SE	P	MHC/SV
DSM-MDD	LifetimeMDD	67171	6	rs926552	29548089	A	G	0.140	0.903	0.019	4.46E-08	MHC
Help-seeking	GPpsy	323344	1	rs6699744	72825144	A	T	0.388	0.960	0.005	6.55E-14	
Help-seeking	GPpsy	332112	1	rs6697602	177039372	G	C	0.083	1.056	0.009	6.36E-09	
Help-seeking	GPpsy	331205	2	rs11123030	124976163	T	C	0.491	1.032	0.005	1.13E-09	
Help-seeking	GPpsy	326346	3	rs66511648	117515519	C	T	0.284	1.033	0.006	2.42E-08	
Help-seeking	GPpsy	329391	5	rs30266	103972357	A	G	0.328	1.039	0.006	3.50E-12	
Help-seeking	GPpsy	331857	6	rs12205083	24275483	G	A	0.104	1.053	0.008	6.24E-10	
Help-seeking	GPpsy	332546	6	rs75782365	26408551	G	T	0.110	0.951	0.008	1.36E-09	MHC
Help-seeking	GPpsy	332629	6	rs7772160	27412386	C	T	0.478	0.965	0.005	3.27E-12	MHC
Help-seeking	GPpsy	332629	6	rs3135296	28795856	T	A	0.120	0.946	0.008	3.75E-12	MHC
Help-seeking	GPpsy	326902	6	rs3115631	29986324	A	T	0.126	0.944	0.008	2.86E-13	MHC
Help-seeking	GPpsy	332629	6	rs1625792	31306420	A	G	0.147	0.961	0.007	4.59E-08	MHC
Help-seeking	GPpsy	327948	6	rs236346	36832103	C	T	0.095	0.950	0.009	1.19E-08	MHC
Help-seeking	GPpsy	331741	6	rs9345737	66676938	G	A	0.439	0.969	0.005	3.03E-09	
Help-seeking	GPpsy	332629	7	rs3807866	12250378	A	G	0.410	1.039	0.005	5.44E-13	
Help-seeking	GPpsy	327847	9	rs393488	17044971	A	T	0.469	0.967	0.005	2.14E-10	
Help-seeking	GPpsy	331280	9	rs12057031	25235063	T	C	0.108	0.952	0.008	5.29E-09	
Help-seeking	GPpsy	322805	10	rs11599236	106454672	C	T	0.408	0.971	0.005	2.91E-08	
Help-seeking	GPpsy	332122	11	rs537635	88705235	T	C	0.484	1.033	0.005	6.24E-10	SV
Help-seeking	GPpsy	329151	11	rs578174	89959637	G	A	0.102	0.953	0.009	2.10E-08	SV

Help-seeking	GPpsy	332489	14	rs12889665	75234830	T	G	0.462	0.972	0.005	3.16E-08	
Help-seeking	GPpsy	329763	14	rs61997596	104511206	A	G	0.191	1.037	0.007	4.15E-08	
Help-seeking	GPpsy	332629	16	rs11646401	21609978	G	C	0.442	1.029	0.005	3.58E-08	
Help-seeking	GPpsy	327186	18	rs12967855	35138245	A	G	0.329	1.034	0.006	1.57E-09	
Help-seeking	GPpsy	331002	18	rs8097498	53449667	G	A	0.387	1.031	0.005	9.58E-09	
Help-seeking	Psypsy	332603	6	rs66975207	26942146	C	A	0.111	0.925	0.013	1.23E-09	MHC
Help-seeking	Psypsy	333419	6	rs4713145	28106827	C	T	0.244	0.941	0.009	5.32E-11	MHC
Help-seeking	Psypsy	333295	6	rs3129120	29111775	C	T	0.124	0.925	0.012	1.45E-10	MHC
Help-seeking	Psypsy	333387	6	rs2517622	30155149	C	G	0.137	0.926	0.012	4.20E-11	MHC
Help-seeking	Psypsy	319776	6	rs535777	32577633	C	G	0.138	0.930	0.012	9.94E-10	MHC
No-MDD	GPNoDep	57572	6	rs3094146	29970960	C	G	0.130	0.870	0.025	4.74E-08	MHC

Supplementary Table 10: Genome-wide significant loci in GWAS for definitions of MDD

This Table shows the genome-wide significant loci (top SNP in 1MB regions) in GWAS using logistic regression for all definitions of MDD in UKBiobank. Only four definitions show genome-wide significant hits: CIDI-based LifetimeMDD, minimal phenotyping, help-seeking based definitions GPpsy and Psypsy, and minimal phenotyping, help-seeking based no-MDD definition that exclude MDD symptoms GPNoDep. For each locus we show the chromosome (CHR), rsid for the top SNP in 1MB window (SNP), position on the chromosome (BP), test and minor allele (A1), major allele (A0), allele frequency of the test allele (A1FREQ) in all White-British samples in UKBiobank, number of samples included in the linear regression at the locus with no missing genotypes, phenotype or covariate data (NMISS), standardized effect size of the minor allele on the phenotype (BETA), standard error of the effect (SE), p-value of the association (P), and whether the locus is in the MHC region on chr6:25-35MB or in any SV regions as listed in Price et al 2008[9] (MHC/SV). We note that rs3094146 in GPNoDep lies in the same locus as rs3115631 in GPpsy, and they lie in the same MB region as rs926552 in LifetimeMDD and rs3129120 in Psypsy, with GPNoDep showing the greatest size of effect (OR=0.84, SE=0.025) demonstrating this locus is not specific to MDD but shared and potentially driven by conditions other than MDD captured by GPNoDep.

CATEGORY	PHENO	NSAMPLES	CHR	SNP	BP	A1	A0	A1FREQ	OR	SE	P	MHC/SV
DSM-MDD	MDD2	63196	6	rs1233396	29546799	A	G	0.140	0.902	0.019	4.79E-08	MHC
DSM-MDD	MDD2recur	55054	5	rs1833718	164635015	T	C	0.364	0.914	0.016	4.01E-08	
Help-seeking	GPpsy	318392	1	rs6699744	72825144	A	T	0.388	0.960	0.005	5.98E-14	
Help-seeking	GPpsy	327022	1	rs6697602	177039372	G	C	0.083	1.056	0.009	5.34E-09	
Help-seeking	GPpsy	326131	2	rs11123030	124976163	T	C	0.491	1.032	0.005	9.95E-10	
Help-seeking	GPpsy	321342	3	rs66511648	117515519	C	T	0.284	1.033	0.006	2.89E-08	
Help-seeking	GPpsy	322712	5	rs40465	103981726	G	T	0.331	1.040	0.006	2.34E-12	
Help-seeking	GPpsy	321888	6	rs3115631	29986324	A	T	0.126	0.942	0.008	5.95E-14	MHC
Help-seeking	GPpsy	327532	6	rs2232423	28366151	G	A	0.117	0.944	0.008	1.73E-12	MHC
Help-seeking	GPpsy	327281	6	rs67859638	27357978	G	A	0.113	0.948	0.008	1.08E-10	MHC
Help-seeking	GPpsy	326771	6	rs12205083	24275483	G	A	0.104	1.053	0.008	1.39E-09	
Help-seeking	GPpsy	326658	6	rs9345737	66676938	G	A	0.439	0.969	0.005	2.97E-09	MHC
Help-seeking	GPpsy	322923	6	rs236346	36832103	C	T	0.095	0.950	0.009	1.13E-08	MHC
Help-seeking	GPpsy	323806	6	rs34158769	26336572	A	G	0.106	0.954	0.009	2.36E-08	MHC
Help-seeking	GPpsy	327532	6	rs1625792	31306420	A	G	0.147	0.960	0.007	3.51E-08	MHC
Help-seeking	GPpsy	327532	7	rs3807866	12250378	A	G	0.410	1.039	0.005	5.11E-13	
Help-seeking	GPpsy	322818	9	rs393488	17044971	A	T	0.469	0.968	0.005	7.69E-10	
Help-seeking	GPpsy	326201	9	rs12057031	25235063	T	C	0.108	0.953	0.008	9.98E-09	
Help-seeking	GPpsy	317841	10	rs11599236	106454672	C	T	0.408	0.970	0.005	2.04E-08	
Help-seeking	GPpsy	321170	11	rs10765180	88740827	T	G	0.482	1.034	0.005	2.35E-10	SV
Help-seeking	GPpsy	324121	11	rs578174	89959637	G	A	0.102	0.953	0.009	2.22E-08	SV
Help-seeking	GPpsy	326354	11	rs4244537	28617622	A	C	0.379	0.971	0.005	4.97E-08	SV
Help-seeking	GPpsy	327394	14	rs12889665	75234830	T	G	0.462	0.972	0.005	2.89E-08	
Help-seeking	GPpsy	324700	14	rs61997596	104511206	A	G	0.191	1.037	0.007	3.64E-08	
Help-seeking	GPpsy	327532	16	rs11646401	21609978	G	C	0.442	1.030	0.005	2.12E-08	
Help-seeking	GPpsy	322176	18	rs12967855	35138245	A	G	0.329	1.034	0.006	1.64E-09	
Help-seeking	GPpsy	325934	18	rs8097498	53449667	G	A	0.387	1.031	0.005	1.05E-08	
Help-seeking	Psypsy	281202	5	rs542852	78409396	T	C	0.362	1.047	0.008	2.82E-08	

Help-seeking	Psypsy	284937	6	rs1235162	29537224	G	A	0.131	0.922	0.012	1.76E-11	MHC
Help-seeking	Psypsy	284937	6	rs4713145	28106827	C	T	0.244	0.941	0.009	6.54E-11	MHC
Help-seeking	Psypsy	273221	6	rs535777	32577633	C	G	0.138	0.929	0.012	6.38E-10	MHC
Help-seeking	Psypsy	284244	6	rs66975207	26942146	C	A	0.111	0.924	0.013	8.87E-10	MHC
Help-seeking	Psypsy	284760	6	rs3095327	30699022	A	G	0.159	0.935	0.011	1.07E-09	MHC
Help-seeking	Psypsy	282552	7	rs6460894	12247330	C	T	0.338	1.048	0.008	1.80E-08	
Help-seeking	Psypsy	284120	14	rs10144051	103885931	A	C	0.287	0.952	0.009	3.07E-08	
No-MDD	GPNoDep	56766	6	rs3094146	29970960	C	G	0.130	0.869	0.025	3.53E-08	MHC

Supplementary Table 11: Genome-wide significant loci in GWAS for definitions of MDD using "clean" controls

This Table shows the genome-wide significant loci (top SNP in 1MB regions) in GWAS for all definitions of MDD in UKBiobank with logistic regression, using "clean" controls rather than all controls. There are more significant loci for GPpsy and Psypsy, and one significant locus for MDDrecur that was not observed in GWAS using all controls at rs1833718. For each locus we show the chromosome (CHR), rsid for the top SNP in 1MB window (SNP), position on the chromosome (BP), test and minor allele (A1), major allele (A0), allele frequency of the test allele (A1FREQ) in all White-British samples in UKBiobank, number of samples included in the linear regression at the locus with no missing genotype, phenotype or covariate data (NMISS), standardized effect size of the minor allele on the phenotype (BETA), standard error of the effect (SE), p-value of the association (P), and whether the locus is in the MHC region on chr6:25-35MB or in any SV regions as listed in Price et al 2008[9] (MHC/SV).

DATAFIELD	QUESTION ON CHILDHOOD TRAUMA "When I was growing up…"	RESPONSE AND SCORE (0/1)						OR for LifetimeMDD
		Prefer not to answer	Never true	Rarely true	Sometimes true	Often true	Very often true	
20487	I felt that someone in my family hated me	NA	0	0	0	1	1	1.799
20488	People in my family hit me so hard that it left me with bruises or marks	NA	0	0	1	1	1	1.215
20489	I felt loved	NA	1	1	1	0	0	1.664
20490	Someone molested me (sexually)	NA	0	1	1	1	1	1.174
20491	There was someone to take me to the doctor if I needed it	Question omitted						

DATAFIELD	QUESTION ON ADULTHOOD TRAUMA "Since I was sixteen…"	RESPONSE AND SCORE (0/1)						OR for LifetimeMDD
		Prefer not to answer	Never true	Rarely true	Sometimes true	Often true	Very often true	
20521	A partner or ex-partner repeatedly belittled me to the extent that I felt worthless	NA	0	0	1	1	1	2.388
20522	I have been in a confiding relationship	NA	1	1	0	0	0	1.039
20525	There was money to pay the rent or mortgage when I needed it	NA	1	1	1	0	0	1.311
20523	A partner or ex-partner deliberately hit me or used violence in any other way	Question omitted						
20524	A partner or ex-partner sexually interfered with me, or forced me to have sex against my wishes	Question omitted						

DATAFIELD	QUESTION FOR LIFETIME TRAUMA "In your life, have you...?"	RESPONSE AND SCORE (0/1)				OR for LifetimeMDD
		Prefer not to answer	Never	Yes, but not in the last 12 months	Yes, within the last 12 months	
20526	Been in a serious accident that you believed to be life-threatening at the time	NA	0	1	1	1.326
20527	Been involved in combat or exposed to a war-zone (either in the military or as a civilian)	Question omitted				
20528	Been diagnosed with a life-threatening illness	NA	0	1	1	1.275
20529	Been attacked, mugged, robbed, or been the victim of a physically violent crime	NA	0	1	1	1.145
20530	Witnessed a sudden violent death (eg. murder, suicide, aftermath of an accident)	NA	0	1	1	1.288
20531	Been a victim of a sexual assault, whether by a stranger or someone you knew	NA	0	1	1	1.339

Supplementary Table 12: Derivation of lifetime trauma score

This table lists questions in the online mental health follow up questionnaire in UKBiobank forming the derivation of lifetime trauma score used in this paper (Supplementary Methods), along with their data field in the UKBiobank data showcase. The questions come in three categories, "Questions on childhood trauma", "Questions on adulthood trauma", and "Question for lifetime trauma". Answers to questions that are of high similarity with another question are excluded from the calculation of lifetime trauma score (Question omitted). We show the multiple-choice answer to each of the questions which indicates a subject as self-reporting having experienced the traumatic life event. We also show the odds ratio (OR) of having experienced each of the traumatic life event on CIDI-based LifetimeMDD, when modelled jointly in a logistic regression with all other traumatic life events, as well as age, sex, years of education, neuroticism, Townsend deprivation index, experience of any traumatic life event in the past 2 years (data field 6145), and total number of traumatic life events reported. We then weight each of the traumatic life events by its OR and sum all weighted scores to arrive at a weighted lifetime trauma score for each individual.

	PHENOTYPE					PCGCs				LDSC		BOLT-REML	
CATEGORY	DEFINITION	OBS PREV	POP PREV	POPPREV ORIGIN	N	H2SNP	SE	COND H2SNP	SE	H2SNP	SE	H2SNP	SE
			0.243	observed prev		0.263	0.022	0.262	0.022	0.189	0.028	0.184	0.012
			0.268	census correction		0.270	0.023	0.269	0.023	0.194	0.029	0.189	0.013
CIDI-based	LifetimeMDD	0.243	0.150	MDD prev = 0.15	67171	0.228	0.019	0.227	0.019	0.163	0.024	0.159	0.011
			0.173	observed prev		0.321	0.026	0.320	0.026	0.228	0.035	0.218	0.016
			0.196	census correction		0.332	0.026	0.331	0.026	0.237	0.036	0.226	0.017
CIDI-based	MDDRecur	0.173	0.150	MDD prev = 0.15	59385	0.306	0.024	0.305	0.024	0.218	0.033	0.208	0.015
			0.266	observed prev		0.185	0.015	0.185	0.015	0.131	0.018	0.132	0.010
			0.279	census correction		0.188	0.015	0.187	0.015	0.132	0.019	0.134	0.010
Symptom	DepAll	0.266	0.150	MDD prev = 0.15	79576	0.157	0.013	0.156	0.012	0.111	0.015	0.112	0.008
			0.078	observed prev		0.110	0.009	0.110	0.009	0.079	0.010	0.077	0.006
			0.084	census correction		0.112	0.009	0.112	0.009	0.081	0.011	0.079	0.006
Self-report	SelfRepDep	0.078	0.150	MDD prev = 0.15	253926	0.135	0.010	0.135	0.010	0.097	0.013	0.095	0.007
			0.043	observed prev		0.127	0.012	0.127	0.012	0.114	0.014	0.075	0.010
			0.043	census correction		0.126	0.011	0.125	0.011	0.114	0.014	0.075	0.010
EMR	ICD10Dep	0.043	0.150	MDD prev = 0.15	212411	0.185	0.017	0.184	0.017	0.164	0.021	0.111	0.014
			0.341	observed prev		0.144	0.008	0.143	0.008	0.120	0.009	0.109	0.003
			0.343	census correction		0.144	0.008	0.144	0.008	0.120	0.009	0.109	0.002
Help-seeking	GPpsy	0.341	0.150	MDD prev = 0.15	332629	0.114	0.007	0.114	0.007	0.096	0.007	0.087	0.002
			0.109	observed prev		0.126	0.012	0.128	0.012	0.103	0.014	0.090	0.004
			0.111	census correction		0.127	0.012	0.126	0.012	0.103	0.014	0.090	0.004
Help-seeking	Psypsy	0.109	0.150	MDD prev = 0.15	333419	0.139	0.014	0.139	0.014	0.113	0.015	0.099	0.004
			0.149	observed prev		0.130	0.028	0.130	0.028	0.084	0.038	0.052	0.015
			0.146	census correction		0.129	0.031	0.129	0.031	0.083	0.038	0.052	0.015
Non-MDD	GPNoDep	0.149	0.150	MDD prev = 0.15	58125	0.130	0.031	0.130	0.031	0.084	0.038	0.052	0.015

Supplementary Table 13: Heritability estimates of definitions of MDD from different methods

This Table shows the h^2_{SNP} estimates of each definition of MDD calculated using three different methods, PCGCs, LDSC, and BOLD-REML, as detailed in Supplementary Methods. For each definition of MDD we show the sample size (N), observed prevalence (PREV), assumed population prevalence (POP PREV), the origin of the assumed population prevalence (POP PREV ORIGIN). We show results from three different assumed population prevalences: the observed prevalence, the census corrected observed prevalence, and previously reported population prevalence of 0.15[8,32]. For each method we show the h^2_{SNP} estimate (H2SNP) and its standard error (SE). For PCGCs, we also show the conditional h^2_{SNP} (COND H2) and its standard error (SE) for completeness [20].

RISK FACTOR	PHENOTYPE		N (PREV)	H2SNP (SE)	N (PREV)	H2SNP (SE)	DIFFERENCE			
	CATEGORY	DEFINITION	AGE >= 60		AGE < 60		ΔH2SNP	DF	T-TEST STAT	T-TEST PVALUE
AGE	CIDI-based	LifetimeMDD	27671 (0.166)	0.298 (0.039)	39500 (0.297)	0.312 (0.027)	0.015	52168	-0.310	3.78E-01
	CIDI-based	MDDRecur	24894 (0.106)	0.256 (0.048)	34491 (0.222)	0.387 (0.038)	0.132	51023	-2.142	1.61E-02
	Symptom	DepAll	38683 (0.224)	0.215 (0.027)	40893 (0.306)	0.232 (0.022)	0.017	76179	-0.503	3.07E-01
	Self-report	SelfRepDep	126331 (0.058)	0.141 (0.016)	127595 (0.098)	0.129 (0.013)	-0.012	243413	0.587	2.79E-01
	EMR	ICD10Dep	107665 (0.036)	0.150 (0.025)	104746 (0.050)	0.170 (0.021)	0.020	205648	-0.604	2.73E-01
	Help-seeking	GPpsy	150368 (0.318)	0.151 (0.014)	182261 (0.359)	0.153 (0.008)	0.002	233073	-0.143	4.43E-01
	Help-seeking	Psypsy	150840 (0.104)	0.150 (0.015)	182579 (0.113)	0.124 (0.012)	-0.026	301479	1.303	9.63E-02
	No-MDD	GPNoDep	29866 (0.152)	0.208 (0.044)	28259 (0.145)	0.153 (0.041)	-0.055	58049	0.920	1.79E-01
DEPRIVATION	CATEGORY	DEFINITION	AGE >= 60		AGE < 60		ΔH2SNP	DF	T-TEST STAT	T-TEST PVALUE
	CIDI-based	LifetimeMDD	13969 (0.304)	0.418 (0.059)	53120 (0.226)	0.252 (0.025)	-0.166	19489	2.596	4.71E-03
	CIDI-based	MDDRecur	12308 (0.239)	0.434 (0.073)	47013 (0.156)	0.338 (0.032)	-0.096	17400	1.212	1.13E-01
	Symptom	DepAll	20435 (0.309)	0.325 (0.038)	59023 (0.251)	0.189 (0.018)	-0.136	30436	3.264	5.50E-04

CATEGORY	DEFINITION	AGE >= 60		AGE < 60		ΔH2SNP	DF	T-TEST STAT	T-TEST PVALUE
Self-report	SelfRepDep	65877 (0.099)	0.178 (0.023)	187750 (0.071)	0.119 (0.011)	-0.059	94849	2.297	1.08E-02
EMR	ICD10Dep	56571 (0.063)	0.216 (0.034)	155596 (0.036)	0.130 (0.017)	0.086	88100	2.276	1.14E-02
Help-seeking	GPpsy	83671 (0.390)	0.149 (0.011)	248566 (0.324)	0.145 (0.008)	-0.004	182828	0.309	3.79E-01
Help-seeking	Psypsy	83835 (0.149)	0.154 (0.016)	249190 (0.095)	0.119 (0.011)	-0.034	172056	1.724	4.23E-02
No-MDD	GPNoDep	14046 (0.168)	0.311 (0.071)	44004 (0.142)	0.143 (0.029)	-0.168	18912	2.203	1.38E-02

	CATEGORY	DEFINITION	AGE >= 60		AGE < 60		ΔH2SNP	DF	T-TEST STAT	T-TEST PVALUE
	CIDI-based	LifetimeMDD	19110 (0.424)	0.401 (0.047)	48057 (0.171)	0.232 (0.025)	-0.169	30581	3.185	7.24E-04
	CIDI-based	MDDRecur	16139 (0.353)	0.468 (0.051)	47013 (0.156)	0.338 (0.032)	-0.130	35988	2.849	2.20E-03
	Symptom	DepAll	8448 (0.408)	0.344 (0.076)	20544 (0.219)	0.295 (0.049)	-0.048	15766	0.535	2.96E-01
TRAUMA	Self-report	SelfRepDep	26454 (0.117)	0.220 (0.047)	54827 (0.057)	0.252 (0.032)	0.032	51237	-0.550	2.91E-01
	EMR	ICD10Dep	21986 (0.049)	0.321 (0.093)	41337 (0.021)	0.286 (0.095)	0.035	58316	0.266	3.95E-01
	Help-seeking	GPpsy	33451 (0.447)	0.233 (0.028)	75790 (0.277)	0.169 (0.015)	-0.064	53301	1.998	2.28E-02
	Help-seeking	Psypsy	33502 (0.160)	0.203 (0.033)	75929 (0.072)	0.193 (0.031)	-0.011	89536	0.238	4.06E-01

CATEGORY	DEFINITION	AGE >= 60		AGE < 60		ΔH2SNP	DF	T-TEST STAT	T-TEST PVALUE
No-MDD	GPNoDep	4980 (0.186)	0.759 (0.181)	16007 (0.119)	0.308 (0.065)	-0.452	6333	2.349	9.43E-03

NEUROTICISM

CATEGORY	DEFINITION	AGE >= 60		AGE < 60		ΔH2SNP	DF	T-TEST STAT	T-TEST PVALUE
CIDI-based	LifetimeMDD	19043 (0.439)	0.381 (0.043)	38003 (0.136)	0.289 (0.030)	-0.092	37284	1.746	4.04E-02
CIDI-based	MDDRecur	16148 (0.370)	0.451 (0.054)	34367 (0.072)	0.315 (0.045)	-0.136	37543	1.948	2.57E-02
Symptom	DepAll	25691 (0.420)	0.212 (0.030)	41428 (0.171)	0.183 (0.027)	-0.029	58976	0.711	2.39E-01
Self-report	SelfRepDep	87606 (0.141)	0.106 (0.013)	117206 (0.027)	0.194 (0.032)	0.088	150998	-2.567	5.12E-03
EMR	ICD10Dep	73570 (0.074)	0.156 (0.023)	97407 (0.042)	0.176 (0.046)	0.020	141169	-0.378	3.53E-01
Help-seeking	GPpsy	110335 (0.513)	0.129 (0.008)	160959 (0.206)	0.115 (0.010)	-0.014	270728	1.067	1.43E-01
Help-seeking	Psypsy	110374 (0.183)	0.118 (0.012)	161225 (0.052)	0.139 (0.015)	0.021	271596	-1.097	1.36E-01
No-MDD	GPNoDep	14841 (0.257)	0.228 (0.054)	34261 (0.088)	0.120 (0.046)	-0.108	35650	1.526	6.35E-02

SEX

CATEGORY	DEFINITION	AGE >= 60		AGE < 60		ΔH2SNP	DF	T-TEST STAT	T-TEST PVALUE
CIDI-based	LifetimeMDD	32933 (0.167)	0.294 (0.039)	34238 (0.315)	0.328 (0.025)	0.033	57293	-0.719	2.36E-01
CIDI-based	MDDRecur	29760 (0.110)	0.360 (0.047)	29625 (0.237)	0.429 (0.033)	0.069	53839	-1.204	1.14E-01
Symptom	DepAll	37728 (0.203)	0.203 (0.034)	41848 (0.323)	0.218 (0.021)	0.015	64013	-0.383	3.51E-01

CATEGORY	DEFINITION	AGE >= 60		AGE < 60		ΔH2SNP	DF	T-TEST STAT	T-TEST PVALUE
Self-report	SelfRepDep	117712 (0.058)	0.133 (0.015)	136214 (0.095)	0.125 (0.012)	-0.008	229531	0.432	3.33E-01
EMR	ICD10Dep	95851 (0.036)	0.171 (0.025)	116560 (0.049)	NA (NA)	NA	NA	NA	NA
Help-seeking	GPpsy	153917 (0.257)	0.149 (0.011)	178712 (0.413)	0.170 (0.009)	0.021	307791	-1.512	6.52E-02
Help-seeking	Psypsy	154190 (0.097)	0.131 (0.016)	179229 (0.119)	0.145 (0.012)	0.014	293736	-0.699	2.42E-01
No-MDD	GPNoDep	29968 (0.112)	0.188 (0.041)	28157 (0.187)	0.228 (0.069)	0.041	46298	-0.507	3.06E-01

EDUCATION	CATEGORY	DEFINITION	AGE >= 60		AGE < 60		ΔH2SNP	DF	T-TEST STAT	T-TEST PVALUE
	CIDI-based	LifetimeMDD	17452 (0.244)	0.356 (0.057)	19815 (0.241)	0.295 (0.042)	-0.061	6872	-2.259	1.20E-02
	CIDI-based	MDDRecur	15446 (0.174)	0.424 (0.071)	17652 (0.174)	0.298 (0.056)	-0.126	6152	-1.607	5.40E-02
	Symptom	DepAll	19804 (0.261)	0.306 (0.044)	33136 (0.256)	0.188 (0.027)	-0.118	19841	-1.055	1.46E-01
	Self-report	SelfRepDep	59341 (0.078)	0.132 (0.027)	115285 (0.077)	0.126 (0.014)	-0.006	70255	-1.419	7.79E-02
	EMR	ICD10Dep	48482 (0.040)	0.205 (0.046)	101513 (0.050)	0.145 (0.020)	0.060	67284	1.207	1.14E-01
	Help-seeking	GPpsy	79630 (0.332)	0.145 (0.013)	144159 (0.353)	0.144 (0.009)	-0.001	128193	-0.890	1.87E-01
	Help-seeking	Psypsy	79791 (0.100)	0.153 (0.024)	144659 (0.114)	NA (NA)	NA	NA	NA	NA

No-MDD	GPNoDep	14570 (0.140)	0.372 (0.117)	24492 (0.164)	0.122 (0.043)	-0.251	14865	-1.277	1.01E-01

Supplementary Table 14: Heritability of definitions of MDD stratified by risk factors

This Table shows the h^2_{SNP} estimates of each definition of MDD calculated using PCGCs in subgroups stratified by risk factors (age, deprivation, trauma, neuroticism, sex and education). For each stratum, we show the number of samples (N_sample), case prevalence (prev), h^2_{SNP} estimate (H2SNP) and its standard error (SE). We show the difference between heritabilities from the two strata per risk factor (ΔH2SNP), and calculate the degree of freedom (DF), t-test statistic (T TEST STAT), and significance of this difference (T TEST PVALUE) using both h^2_{SNP} estimates, standard errors and sample sizes. Items are "NA" when we were not able to get an estimate from PCGCs. None of the differences are significant in a two-tailed t-test at p < 0·05 after multiple testing correction.

Definitions		PCGCs				LDSC						
Definition1	Definition2	rG	rG SE	rho	rho SE	Intercept	rG	rG SE	rho	rho SE	Z Score	P value
ICD10Dep	LifetimeMDD	0.653	0.052	0.119	0.011	0.086	0.646	0.079	0.031	0.004	8.166	3.20E-16
ICD10Dep	MDDRecur	0.685	0.054	0.138	0.012	0.099	0.663	0.082	0.033	0.004	8.120	4.66E-16
ICD10Dep	GPpsy	0.762	0.036	0.103	0.006	0.190	0.798	0.055	0.033	0.003	14.442	2.82E-47
ICD10Dep	Psypsy	0.751	0.041	0.095	0.007	0.211	0.775	0.059	0.023	0.002	13.236	5.42E-40
ICD10Dep	DepAll	0.604	0.056	0.093	0.010	0.094	0.615	0.085	0.025	0.004	7.275	3.46E-13
ICD10Dep	SelfRepDep	0.778	0.050	0.092	0.007	0.265	0.893	0.079	0.021	0.002	11.265	1.94E-29
ICD10Dep	GPNoDep	0.539	0.088	0.069	0.011	0.028	0.662	0.183	0.019	0.004	3.624	3.00E-04
LifetimeMDD	MDDRecur	0.988	0.008	0.287	0.023	0.855	0.999	0.014	0.102	0.015	71.579	0
LifetimeMDD	GPpsy	0.811	0.026	0.158	0.012	0.259	0.903	0.044	0.077	0.008	20.333	6.55E-92
LifetimeMDD	Psypsy	0.772	0.035	0.141	0.015	0.179	0.883	0.054	0.054	0.008	16.254	2.10E-59
LifetimeMDD	DepAll	0.858	0.039	0.189	0.016	0.175	1.011	0.074	0.086	0.010	13.619	3.11E-42
LifetimeMDD	SelfRepDep	0.790	0.043	0.134	0.011	0.170	0.936	0.071	0.045	0.006	13.121	2.48E-39
LifetimeMDD	GPNoDep	0.577	0.078	0.107	0.021	0.042	0.725	0.142	0.043	0.013	5.108	3.26E-07
MDDRecur	GPpsy	0.852	0.029	0.183	0.013	0.245	0.956	0.047	0.083	0.009	20.516	1.55E-93
MDDRecur	Psypsy	0.799	0.040	0.160	0.017	0.186	0.909	0.061	0.057	0.009	14.951	1.52E-50
MDDRecur	DepAll	0.875	0.040	0.213	0.018	0.156	1.072	0.075	0.093	0.011	14.300	2.19E-46
MDDRecur	SelfRepDep	0.845	0.045	0.158	0.013	0.188	0.983	0.075	0.049	0.006	13.184	1.09E-39
MDDRecur	GPNoDep	0.619	0.081	0.126	0.024	0.038	0.809	0.156	0.049	0.015	5.202	1.97E-07
GPpsy	Psypsy	0.903	0.014	0.121	0.010	0.488	0.915	0.019	0.048	0.006	47.077	0
GPpsy	DepAll	0.853	0.027	0.139	0.010	0.410	0.918	0.046	0.067	0.007	20.070	1.34E-89
GPpsy	SelfRepDep	0.859	0.025	0.108	0.007	0.346	0.959	0.044	0.040	0.004	21.760	5.54E-105
GPpsy	GPNoDep	0.840	0.051	0.115	0.014	0.322	1.022	0.160	0.052	0.009	6.410	1.46E-10
Psypsy	DepAll	0.783	0.036	0.119	0.011	0.217	0.878	0.060	0.046	0.007	14.639	1.60E-48
Psypsy	SelfRepDep	0.830	0.029	0.098	0.008	0.326	0.950	0.049	0.028	0.003	19.546	4.50E-85
Psypsy	GPNoDep	0.697	0.069	0.089	0.017	0.092	0.882	0.124	0.032	0.009	7.138	9.50E-13
DepAll	SelfRepDep	0.790	0.044	0.113	0.009	0.151	1.010	0.085	0.041	0.005	11.953	6.27E-33
DepAll	GPNoDep	0.620	0.079	0.096	0.017	0.002	0.875	0.168	0.044	0.011	5.208	1.91E-07

SelfRepDep	GPNoDep	0.587	0.080	0.070	0.013	0.043	0.793	0.139	0.023	0.006	5.703	1.18E-08

Supplementary Table 15: Genetic correlation between definitions of depression in UKBiobank

This Table shows the genetic correlation between definitions of depression in UKBiobank from both PCGCs and LDSC. For each pair of definitions, we show the genetic correlation (rG), its standard error (rG SE), genetic covariance (rho) and its standard error (rho SE) for both methods. In addition, for LDSC, we show the intercept, Z score and P value of the estimation.

CHR	SNP	BP	A1	A0	A1FREQ	NMISS	OR	SE	P	MHC/SV
1	rs1324481	33892964	T	G	0.317	333782	0.9708	0.005	4.01E-08	
1	rs1697593	190453672	T	C	0.483	332979	1.028	0.005	3.70E-08	
1	rs10863714	208710593	A	G	0.4238	335411	1.029	0.005	2.59E-08	
2	rs1004787	45159091	G	A	0.4694	329067	0.9677	0.005	8.80E-11	
2	rs4671381	60496910	T	C	0.4366	334992	0.9728	0.005	4.77E-08	
2	rs67716713	104267572	A	C	0.4866	334796	0.9676	0.005	4.85E-11	
2	rs1427499	145400317	A	G	0.289	336066	1.043	0.006	1.67E-14	
3	rs11711099	25225163	C	T	0.4839	330036	1.029	0.005	1.75E-08	
3	rs591988	61847695	T	C	0.2663	334385	1.032	0.006	4.25E-08	
3	rs73121433	83154013	A	G	0.1632	328418	1.039	0.007	2.01E-08	
3	rs12714592	84387950	C	A	0.2734	335552	1.038	0.006	4.85E-11	SV
3	rs62250491	85616009	G	T	0.3713	333650	1.042	0.005	2.02E-15	SV
3	rs1995245	117776020	C	T	0.1497	333233	0.959	0.007	2.45E-09	
4	rs899632	57749347	C	T	0.3867	332773	0.9702	0.005	4.86E-09	
5	rs1549212	166996722	C	T	0.3744	333822	1.032	0.005	2.22E-09	
6	rs2892512	98744946	C	T	0.2684	334016	1.033	0.006	7.58E-09	
6	rs465646	111620758	G	A	0.1588	334411	1.055	0.007	7.74E-15	
7	rs13237637	3503207	C	G	0.4967	331983	0.9718	0.005	1.41E-08	
7	rs1174864	53127559	G	A	0.4483	334045	0.9726	0.005	3.68E-08	
7	rs2404324	99023461	G	A	0.1547	335670	0.9627	0.007	3.57E-08	
7	rs10244364	117529641	C	T	0.3201	330304	1.039	0.005	1.03E-12	
8	rs13258512	92777433	G	A	0.4221	331316	0.9709	0.005	6.40E-09	
9	rs56209921	38276428	T	C	0.163	335889	1.039	0.007	1.42E-08	
9	rs323740	102083530	G	C	0.4737	335303	0.9706	0.005	2.80E-09	
9	rs7870475	128134034	C	T	0.4743	334109	1.032	0.005	6.28E-10	
10	rs12244388	104640052	A	G	0.3357	335056	1.036	0.005	1.91E-11	
11	rs4756044	45961114	C	A	0.2525	334624	0.9689	0.006	4.10E-08	SV
11	rs10896972	59212884	G	T	0.3302	336010	0.9687	0.005	2.30E-09	

CHR	SNP	BP	A1	A0	A1FREQ	NMISS	OR	SE	P	MHC/SV
11	rs2155290	112851068	G	C	0.3826	335943	1.067	0.005	9.47E-36	
12	rs4766578	111904371	T	A	0.4958	335926	1.028	0.005	3.62E-08	SV
13	rs56081685	59454140	G	T	0.314	335337	0.9704	0.005	2.76E-08	
13	rs837333	101179012	C	T	0.4763	326768	1.029	0.005	1.34E-08	
15	rs150294	89931148	G	A	0.3996	329261	0.9701	0.005	4.04E-09	
17	rs7216173	51891405	A	T	0.2139	323640	1.036	0.006	1.13E-08	
18	rs1221983	49993266	T	G	0.394	335304	1.029	0.005	1.63E-08	

Supplementary Table 16: Genome-wide significant loci in GWAS for smoking

This Table shows the genome-wide significant loci (top SNP in 1MB regions) in GWAS for smoking (data field 20160: "Ever smoked"). For each locus we show the chromosome (CHR), rsid for the top SNP in 1MB window (SNP), position on the chromosome (BP), test and minor allele (A1), major allele (A0), allele frequency of the test allele (A1FREQ) in all White-British samples in UKBiobank, number of samples included in the logistic regression at the locus with no missing genotype, phenotype or covariate data (NMISS), odds ratio of the minor allele on the phenotype (OR), standard error of the OR (SE), p-value of the association (P), and whether the locus is in the MHC region on chr6:25-35MB or in any SV regions as listed in Price et al 2008[9] (MHC/SV).

CHR	SNP	BP	A1	A0	A1FREQ	NMISS	BETA	SE	P	MHC/SV
1	rs1002656	37192741	C	T	0.2905	270132	0.01183	0.001924	7.84E-10	
1	rs4561025	91263757	A	C	0.3521	273426	0.01059	0.001912	3.04E-08	
1	rs12145171	171843249	C	A	0.4283	273985	-0.01105	0.00191	7.22E-09	
2	rs12466146	16077199	T	C	0.4219	271236	0.01055	0.00192	3.88E-08	
2	rs6743916	58704449	A	G	0.2927	271257	-0.01136	0.001921	3.34E-09	
2	rs2042555	148555489	A	G	0.418	273328	0.01323	0.001914	4.77E-12	
2	rs7567451	157053380	G	T	0.2672	272984	-0.01054	0.001915	3.67E-08	
2	rs10497655	185462041	C	T	0.3206	274114	-0.0106	0.001909	2.84E-08	SV
3	rs2278609	16924440	C	T	0.216	270342	0.01191	0.001923	5.86E-10	
3	rs1542212	35683935	G	T	0.3917	271082	0.01205	0.001921	3.54E-10	
3	rs57838764	50374568	C	T	0.1142	273935	0.01062	0.001911	2.75E-08	
3	rs836927	107201428	A	C	0.4257	265524	0.01067	0.001941	3.88E-08	
3	rs10935184	136153468	C	T	0.4093	274114	-0.01165	0.00191	1.06E-09	
4	rs13102162	90939567	G	A	0.3591	264987	-0.01124	0.001942	7.15E-09	
4	rs10032297	139013401	A	T	0.3958	269788	-0.01136	0.001925	3.54E-09	
4	rs7696796	183166469	A	G	0.2464	274114	0.01116	0.00191	5.05E-09	
5	rs4413518	107738001	A	G	0.2189	271136	0.01234	0.00192	1.29E-10	
6	rs2148254	11994762	G	A	0.4928	270744	-0.01133	0.001921	3.67E-09	
6	rs7772160	27412386	C	T	0.4783	274114	-0.01061	0.00191	2.72E-08	MHC
6	rs2269426	32076499	A	G	0.3594	274114	0.01334	0.001911	2.95E-12	MHC
6	rs6916891	98457595	T	G	0.1176	271957	0.01064	0.001917	2.89E-08	
7	rs56226325	2078981	T	C	0.1534	274114	-0.01052	0.00191	3.61E-08	
7	rs11509880	12261911	A	G	0.3278	273194	0.01211	0.001913	2.43E-10	
7	rs73167875	82939096	A	T	0.2022	269308	-0.01083	0.001926	1.90E-08	
7	rs274632	86269181	A	C	0.4229	273225	-0.01153	0.001915	1.71E-09	
7	rs6976111	117495667	A	C	0.2993	264510	0.01101	0.001943	1.45E-08	
7	rs13226841	126389408	C	T	0.4896	274064	0.0125	0.00191	6.03E-11	
8	rs7845515	4946228	A	G	0.2875	265208	0.01267	0.001941	6.69E-11	

8	rs2921036	8363897	T	C	0.4898	269177	0.01775	0.001927	3.32E-20	SV
8	rs477860	9811765	T	C	0.2968	271822	-0.01439	0.001918	6.25E-14	SV
8	rs11250117	10972740	A	C	0.4667	272432	0.0172	0.001915	2.69E-19	SV
9	rs2380937	4145781	C	T	0.4011	272440	-0.01119	0.001916	5.23E-09	
9	rs4977844	23295899	C	G	0.3598	266189	0.01136	0.001937	4.48E-09	
9	rs7869969	96217447	G	A	0.3321	274057	-0.01087	0.00191	1.28E-08	
9	rs28377268	98225056	T	G	0.1071	272736	0.01142	0.001914	2.42E-09	
9	rs2094580	120490857	G	T	0.2825	270567	0.01071	0.001922	2.50E-08	
11	rs34796300	13315205	T	C	0.4254	272562	0.01137	0.001916	2.96E-09	
11	rs297343	16354653	T	G	0.3604	272965	0.01107	0.001914	7.23E-09	
11	rs2071754	31812582	C	T	0.201	274114	0.01262	0.00191	3.94E-11	
11	rs7107356	47676170	A	G	0.4943	273602	-0.01319	0.001911	5.21E-12	SV
11	rs10896636	57448032	G	C	0.3449	268952	0.01281	0.001928	3.02E-11	
11	rs674437	88689953	G	A	0.4843	273301	0.01098	0.001913	9.46E-09	SV
11	rs35738585	113386347	G	T	0.4334	271900	-0.01561	0.001918	3.95E-16	
12	rs11608355	109879292	C	T	0.3132	272760	0.01181	0.001914	6.75E-10	SV
12	rs3741475	117669914	A	G	0.1944	273597	0.01194	0.001911	4.14E-10	
13	rs2210903	69576975	G	A	0.3692	274114	-0.01168	0.00191	9.64E-10	
14	rs4140799	72170969	G	A	0.47	272113	0.01268	0.001917	3.68E-11	
14	rs10144845	75237770	C	T	0.317	274031	-0.01389	0.001911	3.60E-13	
15	rs12903563	78033735	T	C	0.4798	269275	0.01176	0.001927	1.03E-09	
17	rs12938775	2574821	G	A	0.4989	274114	0.0114	0.00191	2.36E-09	
17	rs35982947	38214275	C	A	0.3692	267464	-0.01109	0.001933	9.51E-09	
17	rs62062288	44096553	A	G	0.2181	267423	0.01863	0.001937	6.72E-22	
17	rs56084168	79084574	T	C	0.1478	273326	-0.0123	0.001913	1.27E-10	
18	rs9952522	31286129	C	T	0.4084	272613	-0.01074	0.001915	2.04E-08	
18	rs11665070	35152563	G	A	0.3313	272412	0.01565	0.001916	3.10E-16	
18	rs8097041	50898217	A	T	0.3644	273465	-0.01159	0.001953	2.95E-09	
18	rs56403421	52765283	C	A	0.3309	268579	0.01207	0.001931	4.15E-10	

| 22 | rs1028321 | 39926929 | A | G | 0.3052 | 272405 | -0.0111 | 0.001918 | 7.09E-09 |
| 22 | rs11090045 | 41753603 | A | G | 0.3031 | 263768 | 0.01321 | 0.001945 | 1.13E-11 |

Supplementary Table 17: Genome-wide significant loci in GWAS for neuroticism

This Table shows the genome-wide significant loci (top SNP in 1MB regions) in GWAS for neuroticism score (data field 20127: "Neuroticism score"). For each locus we show the chromosome (CHR), rsid for the top SNP in 1MB window (SNP), position on the chromosome (BP), test and minor allele (A1), major allele (A0), allele frequency of the test allele (A1FREQ) in all White-British samples in UKBiobank, number of samples included in the linear regression at the locus with no missing genotype, phenotype or covariate data (NMISS), standardized effect size of the minor allele on the phenotype (BETA), standard error of the effect (SE), p-value of the association (P), and whether the locus is in the MHC region on chr6:25-35MB or in any SV regions as listed in Price et al 2008[9] (MHC/SV).

CONDITION	CATEGORY	DEFINITION	LDSC				rho-HESS	
			INTERCEPT	RHO (SE)	RG (SE)	P	RHO (SE)	RG (SE)
ADHD	CIDI-based	LifetimeMDD	0.022	0.048 (0.011)	0.297 (0.076)	8.93E-05	0.054 (0.016)	0.271 (0.026)
	Help-seeking	GPpsy	0.026	0.058 (0.007)	0.389 (0.045)	5.47E-18	0.043 (0.008)	0.272 (0.016)
	Symptom	DepAll	0.026	0.038 (0.011)	0.280 (0.081)	5.00E-04	0.044 (0.015)	0.263 (0.029)
	Self-report	SelfRepDep	0.017	0.017 (0.006)	0.227 (0.077)	3.20E-03	0.020 (0.009)	0.217 (0.030)
	EMR	ICD10Dep	0.011	0.039 (0.006)	0.503 (0.072)	3.66E-12	0.030 (0.010)	0.334 (0.035)
	No-MDD	GPNoDep	0.008	0.027 (0.010)	0.307 (0.224)	1.71E-01	0.022 (0.019)	0.206 (0.053)
BIP	CIDI-based	LifetimeMDD	0.019	0.043 (0.013)	0.344 (0.095)	3.00E-04	0.038 (0.012)	0.286 (0.035)
	Help-seeking	GPpsy	0.026	0.033 (0.006)	0.320 (0.052)	5.19E-10	0.028 (0.006)	0.264 (0.021)
	Symptom	DepAll	0.001	0.052 (0.009)	0.534 (0.091)	4.66E-09	0.034 (0.011)	0.290 (0.036)
	Self-report	SelfRepDep	0.021	0.020 (0.005)	0.341 (0.088)	1.00E-04	0.019 (0.007)	0.291 (0.037)
	EMR	ICD10Dep	0.003	0.019 (0.005)	0.306 (0.085)	3.00E-04	0.014 (0.007)	0.225 (0.042)
	No-MDD	GPNoDep	0.003	0.021 (0.011)	0.305 (0.155)	4.87E-02	0.011 (0.014)	0.163 (0.070)
SCZ	CIDI-based	LifetimeMDD	0.023	0.061 (0.010)	0.372 (0.055)	1.38E-11	0.059 (0.008)	0.247 (0.017)
	Help-seeking	GPpsy	0.028	0.046 (0.007)	0.326 (0.037)	5.01E-19	0.038 (0.004)	0.197 (0.010)
	Symptom	DepAll	0.010	0.056 (0.009)	0.421 (0.053)	2.08E-15	0.041 (0.007)	0.201 (0.017)
	Self-report	SelfRepDep	0.019	0.028 (0.005)	0.357 (0.059)	1.11E-09	0.025 (0.004)	0.226 (0.018)
	EMR	ICD10Dep	0.001	0.030 (0.004)	0.354 (0.049)	5.51E-13	0.019 (0.005)	0.180 (0.020)
	No-MDD	GPNoDep	0.006	0.031 (0.010)	0.351 (0.111)	1.60E-03	0.024 (0.009)	0.203 (0.035)
AUT	CIDI-based	LifetimeMDD	0.010	0.030 (0.016)	0.164 (0.090)	6.66E-02	0.039 (0.040)	0.295 (0.077)
	Help-seeking	GPpsy	0.014	0.005 (0.009)	0.033 (0.057)	5.56E-01	0.016 (0.019)	0.147 (0.047)

	Symptom	DepAll	-0.002	0.041 (0.014)	0.272 (0.100)	6.30E-03	0.017 (0.039)	0.146 (0.080)
	Self-report	SelfRepDep	0.007	0.009 (0.009)	0.098 (0.096)	3.06E-01	0.014 (0.023)	0.227 (0.084)
	EMR	ICD10Dep	0.001	-0.008 (0.009)	-0.077 (0.091)	3.98E-01	0.002 (0.025)	0.032 (0.095)
	No-MDD	GPNoDep	0.011	-0.023 (0.017)	-0.225 (0.175)	1.98E-01	0.009 (0.048)	0.146 (0.168)
PGC1-MDD	CIDI-based	LifetimeMDD	0.008	0.107 (0.013)	0.857 (0.127)	1.51E-11	0.076 (0.039)	0.796 (0.099)
	Help-seeking	GPpsy	0.013	0.103 (0.008)	0.940 (0.100)	6.52E-21	0.077 (0.018)	0.996 (0.073)
	Symptom	DepAll	0.003	0.103 (0.012)	0.968 (0.130)	1.12E-13	0.069 (0.037)	0.856 (0.104)
	Self-report	SelfRepDep	0.016	0.050 (0.008)	0.811 (0.124)	6.27E-11	0.048 (0.022)	1.110 (0.117)
	EMR	ICD10Dep	0.010	0.044 (0.007)	0.673 (0.114)	3.80E-09	0.039 (0.024)	0.935 (0.126)
	No-MDD	GPNoDep	-0.003	0.073 (0.013)	1.058 (0.265)	6.46E-05	0.040 (0.046)	0.809 (0.198)
23andMe (depression)	CIDI-based	LifetimeMDD	0.020	0.066 (0.006)	0.826 (0.060)	6.41E-43	0.049 (0.010)	0.512 (0.025)
	Help-seeking	GPpsy	0.045	0.057 (0.003)	0.853 (0.030)	8.74E-179	0.044 (0.004)	0.571 (0.015)
	Symptom	DepAll	0.028	0.048 (0.005)	0.732 (0.064)	3.53E-30	0.041 (0.009)	0.503 (0.028)
	Self-report	SelfRepDep	0.030	0.028 (0.002)	0.735 (0.062)	2.24E-32	0.025 (0.005)	0.568 (0.032)
	EMR	ICD10Dep	0.015	0.023 (0.002)	0.599 (0.066)	1.07E-19	0.018 (0.006)	0.422 (0.035)
	No-MDD	GPNoDep	0.015	0.031 (0.005)	0.680 (0.141)	1.42E-06	0.026 (0.011)	0.533 (0.059)
Neuroticism	CIDI-based	LifetimeMDD	0.179	0.080 (0.007)	0.671 (0.041)	2.69E-60	0.156 (0.009)	1.150 (0.025)
	Help-seeking	GPpsy	0.384	0.072 (0.005)	0.705 (0.019)	1.88E-298	0.147 (0.004)	1.350 (0.015)
	Symptom	DepAll	0.161	0.063 (0.007)	0.617 (0.043)	2.22E-46	0.126 (0.009)	1.090 (0.028)
	Self-report	SelfRepDep	0.231	0.041 (0.004)	0.717 (0.040)	2.48E-71	0.096 (0.005)	1.570 (0.053)
	EMR	ICD10Dep	0.159	0.029 (0.003)	0.499 (0.060)	5.70E-17	0.070 (0.006)	1.210 (0.057)
	No-MDD	GPNoDep	0.109	0.046 (0.007)	0.642 (0.128)	5.69E-07	0.099 (0.011)	1.370 (0.092)

			LDSC			rho-HESS	
	CIDI-based	LifetimeMDD	0.037	0.019 (0.006)	0.192 (0.055)	5.00E-04	0.030 (0.009)	0.283 (0.022)
	Help-seeking	GPpsy	0.071	0.023 (0.004)	0.279 (0.037)	3.95E-14	0.031 (0.004)	0.365 (0.014)
	Symptom	DepAll	0.040	0.023 (0.005)	0.286 (0.057)	5.79E-07	0.031 (0.009)	0.348 (0.025)
Smoking	Self-report	SelfRepDep	0.022	0.008 (0.003)	0.182 (0.052)	5.00E-04	0.012 (0.005)	0.246 (0.026)
	EMR	ICD10Dep	0.016	0.015 (0.002)	0.331 (0.047)	2.55E-12	0.014 (0.006)	0.301 (0.031)
	No-MDD	GPNoDep	0.012	0.015 (0.007)	0.262 (0.100)	8.80E-03	0.015 (0.011)	0.274 (0.045)

Supplementary Table 18: Genetic correlation between definitions of MDD and other conditions

This Table shows the genetic correlation between each definition of MDD in UKBiobank with other conditions: attention deficit hyperactive disorder (ADHD), bipolar disorder (BIP), schizophrenia (SCZ), autism (AUT), first meta-analysis of MDD by PGC (PGC1), minimal phenotyping based MDD study by 23andMe (23andMe), and neuroticism and smoking in UKBiobank. This Table hows results from two different methods: LDSC and rho-HESS. For each of the methods we show the genetic covariance (rho) and its standard error (rho_se), as well as the genetic correlation (rG) and its standard error (rG_se); genetic correlation is genetic covariance divided by the product of the heritabilities of the pair of traits involved. For estimates from LDSC, we show the p-value (P) for the genetic correlation being different from 0. For estimates from rho-HESS, both genetic covariance and genetic correlation are summed from regional genetic covariance and genetic correlations in 1703 independent genomic regions (Supplementary Methods). The Pearson r between rG estimated from LDSC and rho-HESS is 0.70 (P=2.48x10^{-8}).

CATEGORY	PHENOTYPE	SNP	CHR	BP	A1	OR	L95	U95	P	REPLICATION
Help seeking	GPpsy	rs6699744	1	72825144	A	0.960	0.950	0.971	6.55E-14	Replicated
		rs6697602	1	177039372	G	1.056	1.037	1.075	6.36E-09	Replicated
		rs11123030	2	124976163	T	1.032	1.022	1.043	1.13E-09	Replicated
		rs66511648	3	117515519	C	1.033	1.021	1.045	2.42E-08	Replicated
		rs30266	5	103972357	A	1.039	1.028	1.050	3.50E-12	Replicated
		rs12205083	6	24275483	G	1.053	1.036	1.071	6.24E-10	Replicated
		rs75782365	6	26408551	G	0.951	0.936	0.967	1.36E-09	Replicated
		rs7772160	6	27412386	C	0.965	0.955	0.974	3.27E-12	Replicated
		rs4713145	6	28106827	C	0.969	0.957	0.980	1.51E-07	Replicated
		rs3135296	6	28795856	T	0.946	0.931	0.961	3.75E-12	Replicated
		rs3129120	6	29111775	C	0.948	0.934	0.963	1.48E-11	Replicated
		rs3115631	6	29986324	A	0.944	0.929	0.959	2.86E-13	Replicated
		rs2517622	6	30155149	C	0.950	0.936	0.964	1.26E-11	Replicated
		rs1625792	6	31306420	A	0.961	0.947	0.975	4.59E-08	Replicated
		rs535777	6	32577633	C	0.965	0.951	0.980	4.66E-06	Replicated
		rs236346	6	36832103	C	0.950	0.934	0.967	1.19E-08	Replicated
		rs9345737	6	66676938	G	0.969	0.960	0.979	3.03E-09	Replicated
		rs3807866	7	12250378	A	1.039	1.028	1.049	5.44E-13	Replicated
		rs393488	9	17044971	A	0.967	0.958	0.977	2.14E-10	Replicated
		rs12057031	9	25235063	T	0.952	0.936	0.968	5.29E-09	Replicated
		rs11599236	10	106454672	C	0.971	0.961	0.981	2.91E-08	Replicated
		rs537635	11	88705235	T	1.033	1.022	1.043	6.24E-10	Replicated
		rs578174	11	89959637	G	0.953	0.937	0.969	2.10E-08	Replicated
		rs12889665	14	75234830	T	0.972	0.962	0.982	3.16E-08	Replicated
		rs61997596	14	104511206	A	1.037	1.023	1.050	4.15E-08	Replicated
		rs11646401	16	21609978	G	1.029	1.019	1.040	3.58E-08	Replicated
		rs12967855	18	35138245	A	1.034	1.023	1.045	1.57E-09	Replicated
DSM based	LifetimeMDD	rs6699744	1	72825144	A	0.984	0.959	1.010	2.20E-01	NotReplicated
		rs6697602	1	177039372	G	1.061	1.015	1.110	9.30E-03	NotReplicated
		rs11123030	2	124976163	T	1.024	0.999	1.050	6.35E-02	NotReplicated

		rs66511648	3	117515519	C	1.034	1.006	1.064	1.79E-02	NotReplicated
		rs30266	5	103972357	A	1.047	1.020	1.076	6.55E-04	Replicated
		rs12205083	6	24275483	G	0.992	0.952	1.033	6.89E-01	NotReplicated
		rs75782365	6	26408551	G	0.939	0.902	0.978	2.32E-03	NotReplicated
		rs7772160	6	27412386	C	0.957	0.934	0.982	6.19E-04	Replicated
		rs4713145	6	28106827	C	0.962	0.934	0.990	9.04E-03	NotReplicated
		rs3135296	6	28795856	T	0.905	0.870	0.941	5.48E-07	Replicated
		rs3129120	6	29111775	C	0.905	0.871	0.941	4.08E-07	Replicated
		rs3115631	6	29986324	A	0.906	0.872	0.941	4.49E-07	Replicated
		rs2517622	6	30155149	C	0.923	0.890	0.958	2.10E-05	Replicated
		rs1625792	6	31306420	A	0.939	0.906	0.973	4.91E-04	Replicated
		rs535777	6	32577633	C	0.952	0.918	0.988	9.68E-03	NotReplicated
		rs236346	6	36832103	C	0.955	0.915	0.997	3.65E-02	NotReplicated
		rs9345737	6	66676938	G	0.994	0.970	1.020	6.63E-01	NotReplicated
		rs3807866	7	12250378	A	1.049	1.023	1.076	2.33E-04	Replicated
		rs393488	9	17044971	A	0.976	0.952	1.001	6.00E-02	NotReplicated
		rs12057031	9	25235063	T	0.938	0.900	0.977	1.94E-03	NotReplicated
		rs11599236	10	106454672	C	0.970	0.945	0.996	2.13E-02	NotReplicated
		rs537635	11	88705235	T	1.041	1.016	1.068	1.44E-03	Replicated
		rs578174	11	89959637	G	0.974	0.934	1.016	2.17E-01	NotReplicated
		rs12889665	14	75234830	T	0.973	0.949	0.998	3.31E-02	NotReplicated
		rs61997596	14	104511206	A	1.064	1.031	1.099	1.18E-04	Replicated
		rs11646401	16	21609978	G	1.019	0.994	1.045	1.37E-01	NotReplicated
		rs12967855	18	35138245	A	1.001	0.975	1.029	9.23E-01	NotReplicated
No-MDD	**GPNoDep**	rs6699744	1	72825144	A	0.972	0.940	1.006	1.02E-01	NotReplicated
		rs6697602	1	177039372	G	1.073	1.013	1.136	1.61E-02	NotReplicated
		rs11123030	2	124976163	T	1.019	0.986	1.052	2.63E-01	NotReplicated
		rs66511648	3	117515519	C	1.016	0.979	1.053	4.02E-01	NotReplicated
		rs30266	5	103972357	A	1.047	1.012	1.084	8.94E-03	NotReplicated
		rs12205083	6	24275483	G	1.043	0.989	1.099	1.18E-01	NotReplicated
		rs75782365	6	26408551	G	0.907	0.860	0.956	2.98E-04	Replicated

		rs7772160	6	27412386	C	0.930	0.900	0.960	1.05E-05	Replicated
		rs4713145	6	28106827	C	0.919	0.885	0.955	1.33E-05	Replicated
		rs3135296	6	28795856	T	0.881	0.837	0.928	1.49E-06	Replicated
		rs3129120	6	29111775	C	0.895	0.851	0.941	1.54E-05	Replicated
		rs3115631	6	29986324	A	0.869	0.826	0.914	5.62E-08	Replicated
		rs2517622	6	30155149	C	0.891	0.849	0.935	2.80E-06	Replicated
		rs1625792	6	31306420	A	0.913	0.872	0.957	1.38E-04	Replicated
		rs535777	6	32577633	C	0.926	0.882	0.973	2.15E-03	NotReplicated
		rs236346	6	36832103	C	0.990	0.937	1.046	7.21E-01	NotReplicated
		rs9345737	6	66676938	G	0.949	0.919	0.981	1.77E-03	Replicated
		rs3807866	7	12250378	A	1.024	0.991	1.058	1.59E-01	NotReplicated
		rs393488	9	17044971	A	0.964	0.933	0.996	2.86E-02	NotReplicated
		rs12057031	9	25235063	T	0.991	0.940	1.044	7.24E-01	NotReplicated
		rs11599236	10	106454672	C	0.985	0.953	1.019	3.82E-01	NotReplicated
		rs537635	11	88705235	T	0.999	0.967	1.031	9.33E-01	NotReplicated
		rs578174	11	89959637	G	0.962	0.911	1.016	1.66E-01	NotReplicated
		rs12889665	14	75234830	T	0.989	0.957	1.022	5.08E-01	NotReplicated
		rs61997596	14	104511206	A	1.043	1.001	1.087	4.57E-02	NotReplicated
		rs11646401	16	21609978	G	1.047	1.014	1.082	5.11E-03	NotReplicated
		rs12967855	18	35138245	A	1.008	0.974	1.044	6.49E-01	NotReplicated
Other Condition	SCZ	rs6699744	1	72825144	A	0.978	0.956	1.000	4.34E-02	NotReplicated
		rs6697602	1	177039372	G	0.993	0.955	1.030	7.06E-01	NotReplicated
		rs11123030	2	124976163	T	1.026	1.006	1.047	1.36E-02	NotReplicated
		rs66511648	3	117515519	C	0.997	0.973	1.021	8.26E-01	NotReplicated
		rs30266	5	103972357	A	1.023	1.000	1.045	5.02E-02	NotReplicated
		rs12205083	6	24275483	G	0.985	0.952	1.019	3.92E-01	NotReplicated
		rs75782365	6	26408551	G	0.754	0.714	0.794	8.89E-27	Replicated
		rs7772160	6	27412386	C	0.981	0.960	1.001	6.87E-02	NotReplicated
		rs4713145	6	28106827	C	0.923	0.898	0.948	8.73E-09	Replicated
		rs3135296	NA	NA	T	NA	NA	NA	NA	NotReplicated
		rs3129120	NA	NA	C	NA	NA	NA	NA	NotReplicated

		rs3115631	NA	NA	A	NA	NA	NA	NA	NotReplicated
		rs2517622	NA	NA	C	NA	NA	NA	NA	NotReplicated
		rs1625792	NA	NA	A	NA	NA	NA	NA	NotReplicated
		rs535777	6	32577633	C	0.874	0.839	0.910	1.78E-13	Replicated
		rs236346	6	36832103	C	0.999	0.965	1.034	9.72E-01	NotReplicated
		rs9345737	6	66676938	G	0.976	0.955	0.997	2.84E-02	NotReplicated
		rs3807866	7	12250378	A	1.016	0.995	1.037	1.36E-01	NotReplicated
		rs393488	9	17044971	A	0.982	0.961	1.003	9.64E-02	NotReplicated
		rs12057031	9	25235063	T	0.954	0.920	0.989	7.57E-03	NotReplicated
		rs11599236	10	106454672	C	0.961	0.939	0.982	3.63E-04	Replicated
		rs537635	11	88705235	T	1.014	0.993	1.035	1.97E-01	NotReplicated
		rs578174	11	89959637	G	0.989	0.951	1.027	5.83E-01	NotReplicated
		rs12889665	14	75234830	T	0.981	0.960	1.002	7.26E-02	NotReplicated
		rs61997596	14	104511206	A	1.057	1.030	1.085	7.48E-05	Replicated
		rs11646401	16	21609978	G	1.026	1.004	1.048	1.66E-02	NotReplicated
		rs12967855	18	35138245	A	1.015	0.993	1.037	1.77E-01	NotReplicated
		rs6699744	1	72825144	A	0.996	0.986	1.006	4.22E-01	NotReplicated
		rs6697602	1	177039372	G	1.001	0.984	1.019	8.82E-01	NotReplicated
		rs11123030	2	124976163	T	0.998	0.988	1.008	6.74E-01	NotReplicated
		rs66511648	3	117515519	C	1.000	0.990	1.012	9.33E-01	NotReplicated
		rs30266	5	103972357	A	1.020	1.009	1.031	2.01E-04	Replicated
		rs12205083	6	24275483	G	1.005	0.989	1.021	5.48E-01	NotReplicated
Other Condition	Smoking	rs75782365	6	26408551	G	0.967	0.952	0.982	2.55E-05	Replicated
		rs7772160	6	27412386	C	0.982	0.973	0.992	3.08E-04	Replicated
		rs4713145	6	28106827	C	0.978	0.967	0.989	1.53E-04	Replicated
		rs3135296	6	28795856	T	0.970	0.955	0.984	5.95E-05	Replicated
		rs3129120	6	29111775	C	0.970	0.956	0.985	6.00E-05	Replicated
		rs3115631	6	29986324	A	0.979	0.964	0.993	4.67E-03	NotReplicated
		rs2517622	6	30155149	C	0.976	0.962	0.990	6.61E-04	Replicated
		rs1625792	6	31306420	A	0.979	0.966	0.993	3.04E-03	NotReplicated
		rs535777	6	32577633	C	0.981	0.967	0.995	9.58E-03	NotReplicated

		SNP	Chr	Position	Allele	OR	CI_low	CI_high	P	Status
		rs236346	6	36832103	C	0.992	0.976	1.009	3.73E-01	NotReplicated
		rs9345737	6	66676938	G	0.994	0.984	1.004	2.07E-01	NotReplicated
		rs3807866	7	12250378	A	1.004	0.995	1.015	3.78E-01	NotReplicated
		rs393488	9	17044971	A	0.997	0.987	1.007	5.18E-01	NotReplicated
		rs12057031	9	25235063	T	0.982	0.966	0.998	2.29E-02	NotReplicated
		rs11599236	10	106454672	C	0.988	0.978	0.998	1.79E-02	NotReplicated
		rs537635	11	88705235	T	1.009	0.999	1.019	7.48E-02	NotReplicated
		rs578174	11	89959637	G	0.982	0.967	0.999	3.19E-02	NotReplicated
		rs12889665	14	75234830	T	0.988	0.978	0.998	1.38E-02	NotReplicated
		rs61997596	14	104511206	A	1.010	0.997	1.023	1.19E-01	NotReplicated
		rs11646401	16	21609978	G	1.000	0.990	1.010	9.81E-01	NotReplicated
		rs12967855	18	35138245	A	1.011	1.000	1.022	4.10E-02	NotReplicated
		rs6699744	1	72825144	A	0.996	0.993	1.000	5.50E-02	NotReplicated
		rs6697602	1	177039372	G	1.006	1.002	1.010	2.75E-03	NotReplicated
		rs11123030	2	124976163	T	1.006	1.002	1.010	2.23E-03	NotReplicated
		rs66511648	3	117515519	C	1.005	1.001	1.009	1.33E-02	NotReplicated
		rs30266	5	103972357	A	1.009	1.005	1.013	3.75E-06	Replicated
		rs12205083	6	24275483	G	1.008	1.004	1.012	3.17E-05	Replicated
		rs75782365	6	26408551	G	0.992	0.988	0.996	3.35E-05	Replicated
		rs7772160	6	27412386	C	0.989	0.986	0.993	2.72E-08	Replicated
		rs4713145	6	28106827	C	0.993	0.989	0.996	9.14E-05	Replicated
Other Condition	Neuroticism	rs3135296	6	28795856	T	0.991	0.988	0.995	6.03E-06	Replicated
		rs3129120	6	29111775	C	0.992	0.988	0.995	1.53E-05	Replicated
		rs3115631	6	29986324	A	0.992	0.988	0.996	3.67E-05	Replicated
		rs2517622	6	30155149	C	0.993	0.989	0.997	2.15E-04	Replicated
		rs1625792	6	31306420	A	0.994	0.990	0.997	7.07E-04	Replicated
		rs535777	6	32577633	C	0.992	0.988	0.996	4.71E-05	Replicated
		rs236346	6	36832103	C	0.995	0.991	0.999	8.75E-03	NotReplicated
		rs9345737	6	66676938	G	0.997	0.993	1.001	9.08E-02	NotReplicated
		rs3807866	7	12250378	A	1.012	1.008	1.016	9.08E-10	Replicated
		rs393488	9	17044971	A	0.994	0.990	0.998	1.25E-03	Replicated

rs12057031	9	25235063	T	0.995	0.991	0.999	6.92E-03	NotReplicated
rs11599236	10	106454672	C	0.989	0.986	0.993	5.16E-08	Replicated
rs537635	11	88705235	T	1.011	1.007	1.015	1.74E-08	Replicated
rs578174	11	89959637	G	0.994	0.990	0.997	7.41E-04	Replicated
rs12889665	14	75234830	T	0.987	0.983	0.991	9.88E-12	Replicated
rs61997596	14	104511206	A	1.005	1.001	1.009	1.29E-02	NotReplicated
rs11646401	16	21609978	G	1.003	0.999	1.007	1.38E-01	NotReplicated
rs12967855	18	35138245	A	1.015	1.012	1.019	1.47E-15	Replicated

Supplementary Table 19: Effects of GWAS loci from help-seeking definitions on other definitions of MDD in UKBiobank and psychiatric conditions

This Table shows the genome-wide significant loci (top SNP in 1MB regions) in GWAS minimal phenotyping, help-seeking definitions GPpsy and Psypsy and their effects in the following phenotypes: help-seeking definition GPpsy, CIDI-based definition LifetimeMDD, help-seeking no-MDD definition that specifically exclude MDD symptoms GPNoDep, and other psychiatric conditions SCZ, neuroticism and smoking. For each SNP we show the chromosome (CHR), rsid (SNP), position on the chromosome (BP), and test and minor allele (A1). For each SNP-phenotype association we show the odds ratio from logistic regression (OR, in the case of neuroticism which is a quantitative trait, we show exp(BETA) as OR), the lower and upper bounds of the 95% confidence interval of OR (L95 and U95), and the p-value of association (P). An association is considered "Replicated" if its p-value is below $3 \cdot 09 \times 10^{-4}$ (p $< 0 \cdot 05$ after multiple testing correction for 162 tests in total) and its direction of effect is the same as that in the GPpsy and Psypsy, where the association is discovered.

CATEGORY	PHENOTYPE	SNP	CHR	BP	A1	OR	L95	U95	P	REPLICATION
Help seeking	GPpsy	rs301806	1	8482078	C	1.021	1.010	1.031	1.00E-04	Replicated
		rs11209948	1	72811904	G	0.963	0.953	0.973	1.62E-12	Replicated
		rs2422321	1	73293393	G	1.021	1.010	1.032	8.96E-05	Replicated
		rs12065553	1	80793118	G	1.014	1.003	1.025	1.58E-02	NotReplicated
		rs1518395	2	58208074	A	0.989	0.978	0.999	3.21E-02	NotReplicated
		rs1656369	3	158280085	A	0.979	0.969	0.990	1.23E-04	Replicated
		rs10514299	5	87663610	T	1.017	1.005	1.029	4.77E-03	NotReplicated
		rs454214	5	88003403	C	1.018	1.008	1.029	6.71E-04	Replicated
		rs4543289	5	164484948	T	0.977	0.967	0.987	6.52E-06	Replicated
		rs1475120	6	105389953	G	0.981	0.971	0.991	2.71E-04	Replicated
		rs7044150	9	2982931	T	0.987	0.977	0.998	1.90E-02	NotReplicated
		rs6476606	9	37005561	A	1.023	1.012	1.034	2.54E-05	Replicated
		rs10786831	10	106614571	A	1.026	1.015	1.036	1.51E-06	Replicated
		rs2125716	12	84941429	A	1.018	1.006	1.030	4.03E-03	NotReplicated
		rs12552	13	53625781	A	1.011	1.001	1.022	3.25E-02	NotReplicated
		rs8025231	15	37648402	C	1.018	1.008	1.029	5.68E-04	Replicated
		rs2179744	22	41621714	A	1.015	1.004	1.027	7.78E-03	NotReplicated
DSM based	LifetimeMDD	rs301806	1	8482078	C	0.998	0.973	1.023	8.44E-01	NotReplicated
		rs11209948	1	72811904	G	0.977	0.952	1.002	6.88E-02	NotReplicated
		rs2422321	1	73293393	G	1.038	1.012	1.065	4.52E-03	NotReplicated
		rs12065553	1	80793118	G	1.032	1.004	1.060	2.37E-02	NotReplicated
		rs1518395	2	58208074	A	0.990	0.965	1.016	4.63E-01	NotReplicated
		rs1656369	3	158280085	A	0.978	0.952	1.004	8.95E-02	NotReplicated
		rs10514299	5	87663610	T	1.008	0.979	1.037	6.03E-01	NotReplicated
		rs454214	5	88003403	C	1.029	1.003	1.056	2.77E-02	NotReplicated
		rs4543289	5	164484948	T	0.949	0.926	0.974	5.19E-05	Replicated
		rs1475120	6	105389953	G	0.987	0.962	1.012	2.92E-01	NotReplicated
		rs7044150	9	2982931	T	1.006	0.980	1.032	6.77E-01	NotReplicated
		rs6476606	9	37005561	A	1.021	0.995	1.048	1.22E-01	NotReplicated
		rs10786831	10	106614571	A	1.024	0.999	1.051	6.34E-02	NotReplicated

		rs2125716	12	84941429	A	1.013	0.983	1.044	3.97E-01	NotReplicated
		rs12552	13	53625781	A	1.042	1.016	1.068	1.62E-03	Replicated
		rs8025231	15	37648402	C	1.027	1.002	1.053	3.58E-02	NotReplicated
		rs2179744	22	41621714	A	1.044	1.015	1.073	2.47E-03	Replicated
No-MDD	GPNoDep	rs301806	1	8482078	C	0.985	0.953	1.018	3.64E-01	NotReplicated
		rs11209948	1	72811904	G	0.984	0.952	1.017	3.32E-01	NotReplicated
		rs2422321	1	73293393	G	1.014	0.981	1.048	4.16E-01	NotReplicated
		rs12065553	1	80793118	G	0.980	0.946	1.015	2.65E-01	NotReplicated
		rs1518395	2	58208074	A	0.999	0.966	1.032	9.38E-01	NotReplicated
		rs1656369	3	158280085	A	0.984	0.951	1.018	3.61E-01	NotReplicated
		rs10514299	5	87663610	T	1.040	1.002	1.079	4.05E-02	NotReplicated
		rs454214	5	88003403	C	1.020	0.986	1.054	2.49E-01	NotReplicated
		rs4543289	5	164484948	T	0.958	0.928	0.990	9.89E-03	NotReplicated
		rs1475120	6	105389953	G	1.022	0.989	1.056	1.89E-01	NotReplicated
		rs7044150	9	2982931	T	1.005	0.972	1.040	7.61E-01	NotReplicated
		rs6476606	9	37005561	A	0.999	0.966	1.034	9.65E-01	NotReplicated
		rs10786831	10	106614571	A	1.050	1.016	1.085	4.02E-03	NotReplicated
		rs2125716	12	84941429	A	1.045	1.005	1.086	2.57E-02	NotReplicated
		rs12552	13	53625781	A	1.006	0.974	1.040	7.20E-01	NotReplicated
		rs8025231	15	37648402	C	1.023	0.990	1.057	1.74E-01	NotReplicated
		rs2179744	22	41621714	A	1.012	0.976	1.049	5.18E-01	NotReplicated
Other condition	SCZ	rs301806	1	8482078	C	0.946	0.925	0.967	1.38E-06	NotReplicated
		rs11209948	1	72811904	G	0.980	0.958	1.002	7.77E-02	NotReplicated
		rs2422321	1	73293393	G	1.059	1.037	1.080	2.18E-08	Replicated
		rs12065553	1	80793118	G	1.016	0.993	1.039	1.77E-01	NotReplicated
		rs1518395	2	58208074	A	0.942	0.921	0.963	3.43E-08	Replicated
		rs1656369	3	158280085	A	1.000	0.977	1.022	9.72E-01	NotReplicated
		rs10514299	5	87663610	T	0.964	0.940	0.988	2.75E-03	NotReplicated
		rs454214	5	88003403	C	0.973	0.952	0.993	1.09E-02	NotReplicated
		rs4543289	5	164484948	T	0.995	0.974	1.016	6.67E-01	NotReplicated
		rs1475120	6	105389953	G	1.049	1.029	1.070	1.87E-06	NotReplicated

		rs7044150	9	2982931	T	0.985	0.963	1.007	1.74E-01	NotReplicated
		rs6476606	9	37005561	A	0.978	0.956	0.999	4.24E-02	NotReplicated
		rs10786831	10	106614571	A	1.047	1.025	1.068	2.34E-05	Replicated
		rs2125716	12	84941429	A	0.991	0.965	1.016	4.72E-01	NotReplicated
		rs12552	13	53625781	A	0.993	0.972	1.014	5.22E-01	NotReplicated
		rs8025231	15	37648402	C	1.003	0.982	1.024	7.63E-01	NotReplicated
		rs2179744	22	41621714	A	1.064	1.041	1.087	8.31E-08	Replicated
Other condition	Smoking	rs301806	1	8482078	C	0.989	0.979	0.999	2.59E-02	NotReplicated
		rs11209948	1	72811904	G	0.994	0.984	1.004	2.47E-01	NotReplicated
		rs2422321	1	73293393	G	1.012	1.001	1.022	2.44E-02	NotReplicated
		rs12065553	1	80793118	G	1.024	1.013	1.035	1.99E-05	Replicated
		rs1518395	2	58208074	A	0.989	0.979	0.999	2.85E-02	NotReplicated
		rs1656369	3	158280085	A	0.981	0.971	0.991	3.07E-04	Replicated
		rs10514299	5	87663610	T	0.974	0.963	0.985	3.95E-06	NotReplicated
		rs454214	5	88003403	C	0.995	0.985	1.005	3.06E-01	NotReplicated
		rs4543289	5	164484948	T	0.990	0.980	0.999	3.74E-02	NotReplicated
		rs1475120	6	105389953	G	0.999	0.989	1.008	7.76E-01	NotReplicated
		rs7044150	9	2982931	T	0.994	0.984	1.004	2.49E-01	NotReplicated
		rs6476606	9	37005561	A	0.995	0.985	1.005	3.16E-01	NotReplicated
		rs10786831	10	106614571	A	1.006	0.996	1.016	2.40E-01	NotReplicated
		rs2125716	12	84941429	A	1.019	1.007	1.031	1.93E-03	Replicated
		rs12552	13	53625781	A	1.018	1.008	1.028	5.80E-04	Replicated
		rs8025231	15	37648402	C	1.004	0.995	1.014	3.78E-01	NotReplicated
		rs2179744	22	41621714	A	1.000	0.990	1.011	9.40E-01	NotReplicated
Other condition	Neuroticism	rs301806	1	8482078	C	1.009	1.005	1.013	4.26E-06	Replicated
		rs11209948	1	72811904	G	0.997	0.994	1.001	1.56E-01	NotReplicated
		rs2422321	1	73293393	G	1.003	0.999	1.007	1.37E-01	NotReplicated
		rs12065553	1	80793118	G	1.005	1.002	1.009	5.13E-03	NotReplicated
		rs1518395	2	58208074	A	0.991	0.987	0.995	1.38E-06	Replicated
		rs1656369	3	158280085	A	0.995	0.991	0.999	6.42E-03	NotReplicated
		rs10514299	5	87663610	T	1.005	1.001	1.009	7.18E-03	NotReplicated

rs454214	5	88003403	C	1.004	1.001	1.008	2.09E-02	NotReplicated
rs4543289	5	164484948	T	0.992	0.988	0.995	8.95E-06	Replicated
rs1475120	6	105389953	G	0.994	0.990	0.997	7.84E-04	Replicated
rs7044150	9	2982931	T	0.995	0.991	0.999	6.36E-03	NotReplicated
rs6476606	9	37005561	A	1.005	1.001	1.009	6.82E-03	NotReplicated
rs10786831	10	106614571	A	1.007	1.003	1.011	4.39E-04	Replicated
rs2125716	12	84941429	A	1.002	0.999	1.006	2.30E-01	NotReplicated
rs12552	13	53625781	A	1.002	0.999	1.006	2.25E-01	NotReplicated
rs8025231	15	37648402	C	1.003	0.999	1.006	1.67E-01	NotReplicated
rs2179744	22	41621714	A	1.011	1.007	1.015	2.24E-08	Replicated

Supplementary Table 20: Effects of GWAS loci from minimal phenotyping definition of MDD in 23andMe on definitions of MDD in UKBiobank and psychiatric conditions

This Table shows the genome-wide significant loci (top SNP in 1MB regions) in GWAS minimal phenotyping definitions of MDD in 23andMe and their effects in the following phenotypes: help-seeking definition GPpsy, CIDI-based definition LifetimeMDD, help-seeking no-MDD definition that specifically exclude MDD symptoms GPNoDep, and other psychiatric conditions SCZ, neuroticism and smoking. For each SNP we show the chromosome (CHR), rsid (SNP), position on the chromosome (BP), and test and minor allele (A1). For each SNP-phenotype association we show the odds ratio (OR, in the case of neuroticism which is a quantitative trait, we show exp(BETA) as OR), the lower and upper bounds of the 95% confidence interval of OR (L95 and U95), and the p-value of association (P). An association is considered "Replicated' if its p-value is below $4 \cdot 90 \times 10^{-4}$ ($p < 0 \cdot 05$ after multiple testing correction for 102 tests in total) and its direction of effect is the same as that in 23andMe, where the association is discovered.

PGC COHORTS					PRS Analysis		DSM-MDD Criteria A Symptoms		
Name	Cohort	Ncases	Ncontrols	N	Used	Reason Not Used	Symptoms Available	DSM-MDD Cases	% DSM-MDD Cases
BOMA	boma	586	1062	1648	1		Yes	541	92.48
CoFams	cof3	120	126	246	0	N < 500	NA		
PsyCoLaus	col3	507	1445	1952	1		Yes	485	95.85
Edinburgh	edi2	372	285	657	1		No		
GenRED1	gens	1019	1344	2363	1		Yes	1002	98.23
GenPod/Newmeds	gep3	482	2836	3318	1		Yes	233	50.43
Depression Genetic Network (DGN)	grdg	471	470	941	1		Yes	461	97.05
GenRED2	grnd	830	474	1304	1		Yes	808	98.54
GSK/Max Planck Inst Psychiatry	gsk2	880	861	1741	0	PERMISSION	NA		
i2b2	i2b3	806	1067	1873	1		No		
Janssen	jjp2	466	1380	1846	0	PERMISSION	NA		
MPIP/MARS old	mmi2	584	517	1101	1		Yes	291	49.83
MPIP/MARS new	mmo4	264	371	635	1		Yes	113	42.80
NESDA	nes1	1494	1602	3096	1		Yes	1294	94.11
Pfizer	pfm2	281	820	1101	0	PERMISSION	NA		
QIMR	qi3c	864	579	1443	1		Yes	556	95.53
QIMR	qi6c	499	590	1089	1		Yes	465	93.19
QIMR	qio2	565	526	1091	1		Yes	531	93.98
RADIANT-UK	rad3	1872	1528	3400	1		Yes	1552	88.08
RADIANT-GER	rage	322	227	549	1		Yes	297	92.24
RADIANT-Irish	rai2	109	340	449	0	N < 500	NA		
RADIANT-US	rau2	223	378	601	1		Yes	217	97.75
RADIANT-DE	rde4	133	516	649	1		Yes	124	93.94
Roche	roc3	271	92	363	0	PERMISSION	NA		
Rotterdam	rot4	241	1028	1269	1		Yes	113	50.67

Ship0	shp0	366	1087	1453	1	Yes	337	90.35
ShipTrend	shpt	163	484	647	1	No		
STAR*D	stm2	936	934	1870	1	Yes	817	87.57
TwinGene	twg2	1097	2663	3760	1	Yes	806	70.83

Supplementary Table 21: PGC cohorts for out-of-sample predictions of MDD

This Table shows the 29 cohorts in PGC29, as shown in Supplementary Table 3 of Wray et al 2018[32]. We obtained access to 22 of the 29 cohorts through the MDD Working Group of the PGC, and used 20 out of the 22 in our out-of-sample prediction analysis (Used), removing 2 because of their small sample sizes (<500 samples). We indicated the reasons for each of the cohorts we did not use (Reason Not Used). Of note, rad3 is removed from all our analyses post-hoc due to its likely containing individuals that are relatives of individuals in UKBiobank, due to the much higher predictive power in this cohort as compared to other cohorts (see Supplementary Table 21 and Extended Data Figure 6). For each of the cohorts, we indicated their cohort name (Name), abbreviation (Cohort), number of individuals indicated as MDD cases (Ncases), number of individuals indicated as controls (Ncontrols), and total sample size (N). Further, we indicate whether individual level symptom endorsement of DSM-V criterion A symptoms are recorded and available for each cohort (Symptoms Available), and the number of DSM-MDD cases we were able to derive from the individual level symptoms data (DSM-MDD Cases). Using this we calculated the percentage of individuals indicated in the cohort as MDD cases (Ncases) that fulfilled DSM-V criterion A (% DSM-MDD Cases).

PGC Cohorts			Downsampled GPpsy			GPpsy		
			P value threshold = 0.05			P value threshold = 0.05		
Cohort	Nsamples	%Cases DSM-MDD	Nagelkerke's r2 (P)	AUC	h2_Liab (SE)	Nagelkerke's r2 (P)	AUC	h2_Liab (SE)
boma	1648	92.48	1.72E-03 (1.56E-01)	0.51	1.63E-03 (2.22E-03)	1.37E-02 (5.87E-05)	0.56	1.31E-02 (6.26E-03)
col3	1952	95.85	2.07E-06 (9.58E-01)	0.50	2.20E-06 (8.45E-05)	1.96E-02 (3.04E-07)	0.58	2.09E-02 (8.04E-03)
edi2	657	NA	2.04E-04 (7.59E-01)	0.50	1.85E-04 (8.55E-04)	3.48E-02 (5.39E-05)	0.59	3.18E-02 (1.49E-02)
gens	2363	98.24	2.01E-03 (6.10E-02)	0.52	1.82E-03 (1.93E-03)	3.15E-02 (8.70E-14)	0.58	2.88E-02 (7.52E-03)
gep3	3318	50.43	1.13E-03 (1.54E-01)	0.52	1.54E-03 (2.13E-03)	9.56E-03 (3.24E-05)	0.56	1.30E-02 (6.24E-03)
grdg	941	NA	1.00E-05 (9.33E-01)	0.50	8.98E-06 (2.15E-04)	1.85E-02 (2.95E-04)	0.56	1.67E-02 (9.06E-03)
grnd	1304	98.54	2.03E-04 (6.62E-01)	0.51	1.92E-04 (8.69E-04)	2.35E-02 (2.26E-06)	0.58	2.23E-02 (9.23E-03)
i2b3	1873	NA	8.31E-04 (2.89E-01)	0.51	7.55E-04 (1.40E-03)	3.55E-03 (2.83E-02)	0.53	3.23E-03 (2.86E-03)
mmi2	1101	49.83	1.32E-04 (7.42E-01)	0.51	1.18E-04 (7.01E-04)	1.78E-02 (1.23E-04)	0.56	1.61E-02 (8.26E-03)
mmo4	635	42.8	2.14E-03 (3.66E-01)	0.49	1.96E-03 (3.28E-03)	5.98E-03 (1.31E-01)	0.53	5.47E-03 (5.75E-03)
nes1	3096	94.11	2.91E-03 (9.44E-03)	0.53	2.61E-03 (2.00E-03)	1.66E-02 (4.74E-10)	0.56	1.50E-02 (4.75E-03)
qi3c	1443	95.53	4.06E-04 (5.90E-01)	0.51	3.75E-04 (1.37E-03)	1.56E-02 (8.37E-04)	0.56	1.44E-02 (8.48E-03)
qi6c	1089	93.19	8.48E-03 (8.52E-03)	0.55	7.66E-03 (5.77E-03)	1.83E-02 (1.11E-04)	0.56	1.65E-02 (8.43E-03)
qio2	1091	93.98	4.61E-03 (5.23E-02)	0.54	4.14E-03 (4.23E-03)	5.37E-03 (3.62E-02)	0.54	4.83E-03 (4.58E-03)
rad3	3400	88.08	6.20E-03 (1.19E-04)	0.54	5.61E-03 (2.88E-03)	5.46E-02 (9.97E-31)	0.61	4.99E-02 (8.32E-03)
rage	549	92.24	4.38E-03 (1.90E-01)	0.54	4.01E-03 (5.59E-03)	5.84E-03 (1.30E-01)	0.54	5.36E-03 (6.64E-03)
rau2	601	97.75	1.24E-03 (4.62E-01)	0.48	1.16E-03 (3.04E-03)	3.30E-03 (2.30E-01)	0.54	3.10E-03 (5.11E-03)
rde4	649	93.94	1.17E-03 (4.88E-01)	0.52	1.37E-03 (3.85E-03)	1.05E-02 (3.71E-02)	0.55	1.23E-02 (1.18E-02)
rot4	1269	50.67	1.12E-03 (3.48E-01)	0.52	1.35E-03 (2.86E-03)	5.37E-03 (3.94E-02)	0.54	6.50E-03 (6.26E-03)
shp0	1453	90.35	1.05E-06 (9.74E-01)	0.50	1.13E-06 (6.99E-05)	7.18E-03 (7.88E-03)	0.55	7.72E-03 (5.77E-03)
shpt	647	NA	6.00E-04 (6.10E-01)	0.49	6.44E-04 (2.53E-03)	1.46E-02 (1.16E-02)	0.56	1.57E-02 (1.23E-02)
stm2	1870	87.57	2.39E-04 (5.65E-01)	0.51	2.14E-04 (7.34E-04)	4.08E-03 (1.73E-02)	0.53	3.66E-03 (3.03E-03)
twg2	3760	70.83	6.39E-04 (1.95E-01)	0.51	6.48E-04 (1.00E-03)	1.56E-02 (1.30E-10)	0.56	1.59E-02 (4.91E-03)
PGC Cohorts			**Downsampled DepAll**			**DepAll**		
			P value threshold = 0.05			P value threshold = 0.05		
Cohort	Nsamples	%Cases DSM-MDD	Nagelkerke's r2 (P)	AUC	h2_Liab (SE)	Nagelkerke's r2 (P)	AUC	h2_Liab (SE)

| PGC Cohorts | | | Downsampled SelfRepDep | | | SelfRepDep | | |
| | | | P value threshold = 0.05 | | | P value threshold = 0.05 | | |
Cohort	Nsamples	%Cases DSM-MDD	Nagelkerke's r2 (P)	AUC	h2_Liab (SE)	Nagelkerke's r2 (P)	AUC	h2_Liab (SE)
boma	1648	92.48	4.24E-03 (2.57E-02)	0.54	4.04E-03 (3.45E-03)	8.05E-03 (2.11E-03)	0.55	7.66E-03 (4.86E-03)
col3	1952	95.85	1.05E-03 (6.61E-01)	0.53	9.43E-04 (4.19E-03)	3.20E-03 (3.92E-02)	0.53	3.39E-03 (3.28E-03)
edi2	657	NA	9.68E-04 (5.03E-01)	0.51	8.79E-04 (2.55E-03)	1.67E-03 (3.79E-01)	0.52	1.52E-03 (3.06E-03)
gens	2363	98.24	2.80E-03 (2.68E-02)	0.53	2.55E-03 (2.27E-03)	7.63E-03 (2.55E-04)	0.54	6.95E-03 (3.75E-03)
gep3	3318	50.43	7.78E-04 (2.36E-01)	0.52	1.06E-03 (1.79E-03)	3.93E-03 (7.73E-03)	0.54	5.36E-03 (4.00E-03)
grdg	941	NA	1.07E-03 (3.86E-01)	0.51	9.60E-04 (2.20E-03)	7.14E-03 (2.50E-02)	0.55	6.42E-03 (5.66E-03)
grnd	1304	98.54	2.27E-04 (6.43E-01)	0.50	2.15E-04 (9.15E-04)	3.80E-03 (5.82E-02)	0.53	3.59E-03 (3.74E-03)
i2b3	1873	NA	4.84E-03 (1.05E-02)	0.53	4.40E-03 (3.30E-03)	5.95E-03 (4.52E-03)	0.54	5.42E-03 (3.65E-03)
mmi2	1101	49.83	2.03E-04 (6.83E-01)	0.51	1.83E-04 (8.85E-04)	1.39E-03 (2.85E-01)	0.52	1.25E-03 (2.33E-03)
mmo4	635	42.8	1.41E-02 (2.00E-02)	0.55	1.30E-02 (8.55E-03)	2.16E-02 (3.95E-03)	0.54	1.99E-02 (1.17E-02)
nes1	3096	94.11	4.40E-04 (3.13E-01)	0.52	3.95E-04 (7.79E-04)	2.86E-03 (1.01E-02)	0.52	2.57E-03 (1.98E-03)
qi3c	1443	95.53	2.77E-03 (1.60E-01)	0.52	2.55E-03 (3.58E-03)	5.44E-03 (4.86E-02)	0.54	5.03E-03 (5.05E-03)
qi6c	1089	93.19	1.09E-03 (3.46E-01)	0.51	9.86E-04 (2.08E-03)	1.04E-02 (3.62E-03)	0.55	9.37E-03 (6.38E-03)
qio2	1091	93.98	5.20E-05 (8.37E-01)	0.51	4.67E-05 (4.43E-04)	9.18E-04 (3.87E-01)	0.52	8.25E-04 (1.88E-03)
rad3	3400	88.08	4.98E-03 (5.65E-04)	0.53	4.50E-03 (2.59E-03)	1.85E-02 (2.77E-11)	0.57	1.68E-02 (4.95E-03)
rage	549	92.24	4.18E-04 (6.86E-01)	0.52	3.82E-04 (2.16E-03)	3.36E-03 (2.50E-01)	0.52	3.08E-03 (4.91E-03)
rau2	601	97.75	9.96E-04 (5.09E-01)	0.51	9.35E-04 (2.78E-03)	2.26E-03 (3.20E-01)	0.52	2.13E-03 (4.27E-03)
rde4	649	93.94	2.13E-05 (9.25E-01)	0.51	2.49E-05 (5.43E-04)	3.33E-03 (2.42E-01)	0.53	3.89E-03 (6.57E-03)
rot4	1269	50.67	4.97E-04 (5.31E-01)	0.51	6.01E-04 (1.92E-03)	1.31E-04 (7.48E-01)	0.51	1.58E-04 (9.71E-04)
shp0	1453	90.35	8.26E-05 (7.76E-01)	0.50	8.86E-05 (6.31E-04)	2.98E-05 (8.64E-01)	0.50	3.20E-05 (3.85E-04)
shpt	647	NA	8.40E-04 (5.46E-01)	0.52	9.02E-04 (2.93E-03)	9.25E-03 (4.47E-02)	0.55	9.94E-03 (9.72E-03)
stm2	1870	87.57	7.34E-04 (3.13E-01)	0.52	6.59E-04 (1.27E-03)	5.26E-03 (6.84E-03)	0.54	4.72E-03 (3.43E-03)
twg2	3760	70.83	3.08E-03 (4.41E-03)	0.53	3.13E-03 (2.19E-03)	4.01E-03 (1.17E-03)	0.53	4.07E-03 (2.50E-03)
boma	1648	92.48	1.25E-03 (2.26E-01)	0.53	1.19E-03 (1.90E-03)	8.72E-03 (1.38E-03)	0.55	8.30E-03 (5.02E-03)
col3	1952	95.85	5.61E-04 (7.49E-01)	0.52	5.03E-04 (3.26E-03)	2.74E-03 (5.64E-02)	0.48	2.90E-03 (3.04E-03)
edi2	657	NA	1.31E-03 (4.36E-01)	0.50	1.19E-03 (2.80E-03)	5.48E-03 (1.11E-01)	0.54	4.98E-03 (5.81E-03)

Cohort	Nsamples	%Cases DSM-MDD	Nagelkerke's r2 (P)	AUC	h2_Liab (SE)	Nagelkerke's r2 (P)	AUC	h2_Liab (SE)
gens	2363	98.24	3.39E-03 (1.49E-02)	0.54	3.08E-03 (2.50E-03)	8.10E-03 (1.65E-04)	0.55	7.37E-03 (3.87E-03)
gep3	3318	50.43	2.71E-03 (2.70E-02)	0.53	3.70E-03 (3.34E-03)	1.60E-03 (8.92E-02)	0.53	2.18E-03 (2.57E-03)
grdg	941	NA	7.72E-05 (8.16E-01)	0.50	6.92E-05 (5.99E-04)	9.44E-03 (9.92E-03)	0.55	8.49E-03 (6.47E-03)
grnd	1304	98.54	4.78E-04 (5.02E-01)	0.52	4.51E-04 (1.34E-03)	2.72E-03 (1.09E-01)	0.54	2.56E-03 (3.18E-03)
i2b3	1873	NA	7.24E-04 (3.22E-01)	0.52	6.58E-04 (1.32E-03)	1.31E-03 (1.84E-01)	0.52	1.19E-03 (1.75E-03)
mmi2	1101	49.83	5.22E-06 (9.48E-01)	0.51	4.70E-06 (1.42E-04)	2.14E-03 (1.85E-01)	0.48	1.92E-03 (2.88E-03)
mmo4	635	42.8	5.45E-03 (1.49E-01)	0.53	4.99E-03 (5.50E-03)	1.11E-02 (3.92E-02)	0.55	1.02E-02 (8.07E-03)
nes1	3096	94.11	2.37E-03 (1.91E-02)	0.53	2.13E-03 (1.81E-03)	4.55E-03 (1.16E-03)	0.53	4.09E-03 (2.50E-03)
qi3c	1443	95.53	3.28E-05 (8.78E-01)	0.50	3.03E-05 (3.81E-04)	5.45E-04 (5.33E-01)	0.51	5.03E-04 (1.62E-03)
qi6c	1089	93.19	2.81E-03 (1.30E-01)	0.52	2.54E-03 (3.33E-03)	7.98E-04 (4.20E-01)	0.52	7.20E-04 (1.78E-03)
qio2	1091	93.98	7.24E-07 (9.81E-01)	0.51	6.50E-07 (9.02E-05)	3.77E-06 (9.56E-01)	0.50	3.38E-06 (9.47E-05)
rad3	3400	88.08	4.96E-03 (5.79E-04)	0.54	4.49E-03 (2.58E-03)	1.69E-02 (1.89E-10)	0.56	1.53E-02 (4.73E-03)
rage	549	92.24	3.41E-03 (2.47E-01)	0.54	3.12E-03 (5.07E-03)	1.58E-05 (9.37E-01)	0.51	1.45E-05 (3.36E-04)
rau2	601	97.75	3.52E-03 (2.15E-01)	0.52	3.30E-03 (5.18E-03)	9.16E-05 (8.41E-01)	0.51	8.60E-05 (8.66E-04)
rde4	649	93.94	5.59E-04 (6.32E-01)	0.50	6.54E-04 (2.96E-03)	4.27E-04 (6.75E-01)	0.53	4.99E-04 (2.34E-03)
rot4	1269	50.67	7.01E-03 (1.86E-02)	0.54	8.48E-03 (7.17E-03)	3.32E-03 (1.05E-01)	0.53	4.02E-03 (4.94E-03)
shp0	1453	90.35	1.13E-03 (2.92E-01)	0.52	1.21E-03 (2.28E-03)	5.86E-04 (4.48E-01)	0.51	6.29E-04 (1.65E-03)
shpt	647	NA	3.38E-03 (2.26E-01)	0.53	3.63E-03 (5.86E-03)	5.95E-03 (1.08E-01)	0.53	6.39E-03 (7.84E-03)
stm2	1870	87.57	3.48E-03 (2.79E-02)	0.53	3.12E-03 (2.81E-03)	3.68E-03 (2.38E-02)	0.53	3.30E-03 (2.87E-03)
twg2	3760	70.83	2.13E-03 (1.80E-02)	0.53	2.16E-03 (1.82E-03)	8.91E-03 (1.27E-06)	0.55	9.06E-03 (3.71E-03)
PGC Cohorts			**Downsampled ICD10Dep**			**ICD10Dep**		
			P value threshold = 0.05			**P value threshold = 0.05**		
Cohort	**Nsamples**	**%Cases DSM-MDD**	**Nagelkerke's r2 (P)**	**AUC**	**h2_Liab (SE)**	**Nagelkerke's r2 (P)**	**AUC**	**h2_Liab (SE)**
boma	1648	92.48	6.89E-04 (3.69E-01)	0.49	6.54E-04 (1.35E-03)	3.96E-03 (3.13E-02)	0.53	3.76E-03 (3.37E-03)
col3	1952	95.85	6.49E-04 (7.30E-01)	0.51	5.82E-04 (3.68E-03)	2.83E-05 (8.46E-01)	0.50	3.00E-05 (3.12E-04)
edi2	657	NA	9.01E-03 (4.08E-02)	0.53	8.19E-03 (7.94E-03)	1.42E-02 (1.03E-02)	0.54	1.29E-02 (9.79E-03)
gens	2363	98.24	1.49E-03 (1.06E-01)	0.52	1.36E-03 (1.66E-03)	5.04E-03 (2.97E-03)	0.53	4.59E-03 (3.05E-03)
gep3	3318	50.43	1.46E-03 (1.05E-01)	0.53	1.99E-03 (2.43E-03)	5.39E-04 (3.25E-01)	0.52	7.34E-04 (1.48E-03)
grdg	941	NA	7.75E-03 (1.95E-02)	0.55	6.97E-03 (5.88E-03)	1.39E-02 (1.76E-03)	0.55	1.25E-02 (7.84E-03)

Cohort	Nsamples	%Cases DSM-MDD	Nagelkerke's r2 (P)	AUC	h2_Liab (SE)	Nagelkerke's r2 (P)	AUC	h2_Liab (SE)
grnd	1304	98.54	7.46E-04 (4.02E-01)	0.51	7.04E-04 (1.65E-03)	4.37E-03 (4.22E-02)	0.53	4.13E-03 (4.03E-03)
i2b3	1873	NA	5.51E-03 (6.32E-03)	0.53	5.01E-03 (3.53E-03)	1.01E-02 (2.08E-04)	0.55	9.24E-03 (4.80E-03)
mmi2	1101	49.83	2.35E-03 (1.64E-01)	0.52	2.11E-03 (3.02E-03)	5.11E-03 (4.03E-02)	0.53	4.60E-03 (4.44E-03)
mmo4	635	42.8	6.52E-03 (1.14E-01)	0.52	5.97E-03 (6.17E-03)	7.48E-03 (9.08E-02)	0.52	6.85E-03 (6.63E-03)
nes1	3096	94.11	1.59E-03 (5.53E-02)	0.52	1.42E-03 (1.48E-03)	2.59E-03 (1.43E-02)	0.53	2.33E-03 (1.89E-03)
qi3c	1443	95.53	4.67E-03 (6.78E-02)	0.53	4.31E-03 (4.67E-03)	5.48E-04 (5.32E-01)	0.50	5.06E-04 (1.59E-03)
qi6c	1089	93.19	1.21E-04 (7.54E-01)	0.50	1.09E-04 (6.96E-04)	5.75E-04 (4.94E-01)	0.51	5.18E-04 (1.51E-03)
qio2	1091	93.98	1.49E-05 (9.12E-01)	0.50	1.34E-05 (2.66E-04)	2.21E-03 (1.80E-01)	0.53	1.98E-03 (2.94E-03)
rad3	3400	88.08	6.04E-03 (1.47E-04)	0.54	5.46E-03 (2.84E-03)	1.08E-02 (3.59E-07)	0.55	9.80E-03 (3.79E-03)
rage	549	92.24	1.22E-03 (4.89E-01)	0.54	1.12E-03 (3.20E-03)	5.92E-03 (1.27E-01)	0.55	5.43E-03 (6.97E-03)
rau2	601	97.75	4.74E-03 (1.50E-01)	0.53	4.45E-03 (6.04E-03)	4.25E-06 (9.66E-01)	0.50	3.99E-06 (1.72E-04)
rde4	649	93.94	9.95E-05 (8.40E-01)	0.50	1.16E-04 (1.07E-03)	2.65E-04 (7.41E-01)	0.50	3.10E-04 (1.95E-03)
rot4	1269	50.67	4.07E-04 (5.71E-01)	0.52	4.91E-04 (1.73E-03)	6.80E-06 (9.42E-01)	0.50	8.21E-06 (2.18E-04)
shp0	1453	90.35	2.72E-03 (1.02E-01)	0.53	2.92E-03 (3.55E-03)	2.38E-03 (1.26E-01)	0.53	2.56E-03 (3.32E-03)
shpt	647	NA	4.92E-03 (1.43E-01)	0.53	5.29E-03 (7.08E-03)	1.74E-04 (7.83E-01)	0.50	1.87E-04 (1.28E-03)
stm2	1870	87.57	1.41E-06 (9.65E-01)	0.51	1.27E-06 (4.77E-05)	1.19E-03 (1.99E-01)	0.51	1.07E-03 (1.65E-03)
twg2	3760	70.83	3.39E-03 (2.81E-03)	0.53	3.45E-03 (2.29E-03)	2.72E-03 (7.51E-03)	0.53	2.76E-03 (2.05E-03)
PGC Cohorts			**Downsampled LifetimeMDD**			**LifetimeMDD**		
			P value threshold = 0.05			**P value threshold = 0.05**		
Cohort	**Nsamples**	**%Cases DSM-MDD**	**Nagelkerke's r2 (P)**	**AUC**	**h2_Liab (SE)**	**Nagelkerke's r2 (P)**	**AUC**	**h2_Liab (SE)**
boma	1648	92.48	1.96E-03 (1.30E-01)	0.51	1.86E-03 (2.38E-03)	1.66E-03 (1.63E-01)	0.48	1.58E-03 (2.18E-03)
col3	1952	95.85	1.71E-02 (7.60E-02)	0.56	1.54E-02 (1.72E-02)	2.54E-03 (6.58E-02)	0.52	2.70E-03 (2.93E-03)
edi2	657	NA	5.81E-03 (1.01E-01)	0.54	5.28E-03 (6.12E-03)	7.46E-03 (6.28E-02)	0.54	6.78E-03 (6.86E-03)
gens	2363	98.24	4.47E-03 (5.13E-03)	0.53	4.07E-03 (2.88E-03)	9.27E-03 (5.54E-05)	0.55	8.44E-03 (4.13E-03)
gep3	3318	50.43	1.34E-03 (1.20E-01)	0.48	1.83E-03 (2.36E-03)	2.65E-03 (2.90E-02)	0.52	3.60E-03 (3.28E-03)
grdg	941	NA	1.68E-03 (2.78E-01)	0.52	1.50E-03 (2.75E-03)	9.01E-03 (1.18E-02)	0.55	8.10E-03 (6.33E-03)
grnd	1304	98.54	5.97E-03 (1.76E-02)	0.54	5.63E-03 (4.69E-03)	4.21E-03 (4.61E-02)	0.53	3.98E-03 (3.97E-03)
i2b3	1873	NA	3.99E-03 (2.01E-02)	0.53	3.63E-03 (2.99E-03)	4.36E-03 (1.51E-02)	0.54	3.96E-03 (3.18E-03)
mmi2	1101	49.83	2.41E-03 (1.60E-01)	0.52	2.17E-03 (3.05E-03)	1.71E-03 (2.36E-01)	0.48	1.54E-03 (2.55E-03)

Cohort	Nsamples	%Cases DSM-MDD	Nagelkerke's r2 (P)	AUC	h2_Liab (SE)	Nagelkerke's r2 (P)	AUC	h2_Liab (SE)
mmo4	635	42.8	8.39E-04 (5.71E-01)	0.52	7.68E-04 (2.22E-03)	2.57E-04 (7.54E-01)	0.52	2.35E-04 (1.93E-03)
nes1	3096	94.11	5.77E-03 (2.52E-04)	0.54	5.19E-03 (2.82E-03)	1.25E-02 (6.97E-08)	0.55	1.13E-02 (4.13E-03)
qi3c	1443	95.53	7.03E-03 (2.50E-02)	0.54	6.49E-03 (5.74E-03)	1.74E-02 (4.17E-04)	0.57	1.61E-02 (8.98E-03)
qi6c	1089	93.19	1.21E-02 (1.67E-03)	0.56	1.09E-02 (6.88E-03)	1.12E-02 (2.45E-03)	0.55	1.02E-02 (6.64E-03)
qio2	1091	93.98	1.38E-04 (7.37E-01)	0.51	1.24E-04 (7.64E-04)	3.51E-03 (9.07E-02)	0.53	3.15E-03 (3.66E-03)
rad3	3400	88.08	4.20E-03 (1.55E-03)	0.53	3.80E-03 (2.37E-03)	8.75E-03 (4.81E-06)	0.54	7.92E-03 (3.43E-03)
rage	549	92.24	9.03E-03 (5.93E-02)	0.55	8.28E-03 (8.38E-03)	5.38E-03 (1.46E-01)	0.53	4.93E-03 (6.75E-03)
rau2	601	97.75	1.14E-02 (2.52E-02)	0.55	1.07E-02 (9.32E-03)	1.06E-02 (3.13E-02)	0.55	9.95E-03 (9.01E-03)
rde4	649	93.94	8.15E-03 (6.69E-02)	0.55	9.55E-03 (1.03E-02)	3.28E-03 (2.46E-01)	0.52	3.84E-03 (6.53E-03)
rot4	1269	50.67	4.40E-06 (9.53E-01)	0.51	5.31E-06 (1.79E-04)	2.44E-03 (1.65E-01)	0.53	2.95E-03 (4.23E-03)
shp0	1453	90.35	6.59E-04 (4.21E-01)	0.51	7.08E-04 (1.75E-03)	1.97E-03 (1.65E-01)	0.52	2.11E-03 (3.02E-03)
shpt	647	NA	2.51E-03 (2.97E-01)	0.53	2.69E-03 (5.07E-03)	5.65E-03 (1.17E-01)	0.54	6.08E-03 (7.52E-03)
stm2	1870	87.57	1.33E-03 (1.74E-01)	0.52	1.19E-03 (1.74E-03)	7.02E-04 (3.24E-01)	0.51	6.30E-04 (1.25E-03)
twg2	3760	70.83	2.58E-03 (9.21E-03)	0.53	2.62E-03 (2.01E-03)	8.77E-03 (1.52E-06)	0.55	8.92E-03 (3.68E-03)
PGC Cohorts			**Downsampled GPNoDep**			**GPNoDep**		
			P value threshold = 0.05			**P value threshold = 0.05**		
Cohort	Nsamples	%Cases DSM-MDD	Nagelkerke's r2 (P)	AUC	h2_Liab (SE)	Nagelkerke's r2 (P)	AUC	h2_Liab (SE)
boma	1648	92.48	3.91E-07 (9.83E-01)	0.51	3.71E-07 (8.97E-06)	6.75E-04 (3.74E-01)	0.52	6.41E-04 (1.41E-03)
col3	1952	95.85	3.09E-07 (9.94E-01)	0.52	2.78E-07 (1.31E-04)	2.64E-03 (6.11E-02)	0.53	2.80E-03 (2.98E-03)
edi2	657	NA	7.65E-04 (5.52E-01)	0.51	6.95E-04 (2.51E-03)	4.80E-03 (1.36E-01)	0.54	4.36E-03 (6.00E-03)
gens	2363	98.24	3.21E-06 (9.40E-01)	0.51	2.92E-06 (8.04E-05)	2.08E-05 (8.49E-01)	0.50	1.89E-05 (1.95E-04)
gep3	3318	50.43	5.43E-04 (3.23E-01)	0.52	7.40E-04 (1.51E-03)	2.46E-05 (8.33E-01)	0.50	3.35E-05 (3.25E-04)
grdg	941	NA	6.06E-03 (3.90E-02)	0.54	5.44E-03 (5.21E-03)	1.13E-02 (4.68E-03)	0.56	1.02E-02 (7.11E-03)
grnd	1304	98.54	2.11E-03 (1.58E-01)	0.52	1.99E-03 (2.78E-03)	6.56E-04 (4.31E-01)	0.51	6.20E-04 (1.56E-03)
i2b3	1873	NA	1.52E-03 (1.52E-01)	0.51	1.38E-03 (1.86E-03)	3.94E-03 (2.10E-02)	0.53	3.58E-03 (2.98E-03)
mmi2	1101	49.83	1.85E-05 (9.02E-01)	0.51	1.67E-05 (2.80E-04)	3.94E-04 (5.69E-01)	0.50	3.55E-04 (1.22E-03)
mmo4	635	42.8	3.48E-03 (2.49E-01)	0.53	3.19E-03 (3.81E-03)	2.91E-04 (7.39E-01)	0.51	2.66E-04 (5.17E-04)
nes1	3096	94.11	8.79E-04 (1.54E-01)	0.51	7.90E-04 (1.10E-03)	1.15E-03 (1.03E-01)	0.52	1.03E-03 (1.26E-03)
qi3c	1443	95.53	1.26E-04 (7.64E-01)	0.50	1.16E-04 (7.70E-04)	1.32E-03 (3.32E-01)	0.52	1.22E-03 (2.49E-03)

Cohort	N	% Cases DSM-MDD	r² (P)	AUC	h2PRS_Liab (SE)	r² (P)	AUC	h2PRS_Liab (SE)
qi6c	1089	93.19	2.31E-03 (1.70E-01)	0.52	2.09E-03 (3.03E-03)	1.14E-03 (3.35E-01)	0.51	1.03E-03 (2.13E-03)
qio2	1091	93.98	2.55E-03 (1.49E-01)	0.53	2.29E-03 (3.12E-03)	1.23E-03 (3.16E-01)	0.52	1.11E-03 (2.19E-03)
rad3	3400	88.08	3.39E-03 (4.49E-03)	0.53	3.06E-03 (2.13E-03)	4.68E-03 (8.30E-04)	0.53	4.23E-03 (2.50E-03)
rage	549	92.24	2.27E-03 (3.45E-01)	0.52	2.08E-03 (3.81E-03)	1.73E-03 (4.10E-01)	0.52	1.58E-03 (3.40E-03)
rau2	601	97.75	4.48E-03 (1.61E-01)	0.54	4.21E-03 (5.98E-03)	4.50E-03 (1.60E-01)	0.54	4.23E-03 (5.99E-03)
rde4	649	93.94	1.42E-03 (4.45E-01)	0.52	1.66E-03 (4.47E-03)	2.04E-04 (7.72E-01)	0.50	2.38E-04 (1.54E-03)
rot4	1269	50.67	1.83E-03 (2.29E-01)	0.52	2.22E-03 (3.67E-03)	2.46E-03 (1.64E-01)	0.53	2.97E-03 (4.25E-03)
shp0	1453	90.35	7.55E-06 (9.31E-01)	0.50	8.11E-06 (1.76E-04)	4.98E-05 (8.25E-01)	0.50	5.35E-05 (4.76E-04)
shpt	647	NA	9.24E-04 (5.26E-01)	0.51	9.92E-04 (3.15E-03)	5.93E-03 (1.08E-01)	0.53	6.37E-03 (7.83E-03)
stm2	1870	87.57	2.77E-04 (5.35E-01)	0.50	2.48E-04 (7.96E-04)	4.21E-05 (8.09E-01)	0.51	3.77E-05 (3.06E-04)
twg2	3760	70.83	2.65E-04 (4.04E-01)	0.49	2.68E-04 (6.41E-04)	3.59E-05 (7.59E-01)	0.50	3.64E-05 (2.34E-04)

Supplementary Table 22: Out-of-sample prediction of MDD in PGC cohorts

This Table shows the prediction of MDD status indicated in 20 PGC cohorts with polygenic risk scores (PRS) computed from GWAS summary statistics of definitions of depression in UKBiobank. The PRS are calculated using effect sizes at independent (LD r2 < 0.1) SNPs passing P-value thresholds 0.05 only (for results at other P-value thresholds, see Figure 7 and Supplementary Figure 13,15). We show results from PRS computed from GWAS performed on down-sampled cases and controls ("Downsampled"), as well as on all cases and controls. For each cohort in PGC we show the cohort name (Cohort), number of samples (N) and percentage of cases that fulfill DSM-V criterion A for symptoms (% Cases DSM-MDD). For prediction results from each definition of depression in UKBiobank, we show the Nagelkerke's r^2 with the P-value of correlation (P), the area under the curve for prediction accuracy (AUC) and variance of MDD status explained by the PRS under the liability scale, assuming population prevalence of 0.15 (h2PRS_Liab) with its standard error (SE). We draw attention to results in cohort rad3, which has much higher Nagelkerke's r^2 and AUC than other cohorts at each P value threshold, likely due to it containing relatives of individuals in the UKBiobank, being a UK-based cohort. We removed this cohort from the calculation of prediction accuracy across all cohorts.

Category	Definition	PRS P value threshold	Correlation between % DSM-MDD Cases in PGC Cohorts and PRS		
			Pearson r	Pearson r2	P value
Help-seeking	GPpsy	0.05	0.290	0.084	0.229
		0.1	0.138	0.019	0.574
		0.2	0.056	0.003	0.820
		0.5	-0.044	0.002	0.857
		1	-0.069	0.005	0.778
Symptom	DepAll	0.05	0.290	0.084	0.229
		0.1	0.138	0.019	0.574
		0.2	0.056	0.003	0.820
		0.5	-0.044	0.002	0.857
		1	-0.069	0.005	0.778
Self-report	SelfRepDep	0.05	-0.231	0.053	0.342
		0.1	-0.152	0.023	0.534
		0.2	-0.172	0.029	0.482
		0.5	-0.130	0.017	0.596
		1	-0.138	0.019	0.572
EMR	ICD10Dep	0.05	-0.016	0.000	0.949
		0.1	-0.321	0.103	0.180
		0.2	-0.356	0.127	0.134
		0.5	-0.210	0.044	0.388
		1	-0.235	0.055	0.332
DSM-based	LifetimeMDD	0.05	0.448	0.200	0.055
		0.1	0.512	0.262	0.025
		0.2	0.438	0.192	0.061
		0.5	0.425	0.181	0.070
		1	0.419	0.175	0.074
No-MDD	GPNoDep	0.05	-0.016	0.000	0.949
		0.1	-0.321	0.103	0.180
		0.2	-0.356	0.127	0.134
		0.5	-0.210	0.044	0.388
		1	-0.235	0.055	0.332

Supplementary Table 23: Correlation between prediction Naglekerke's r2 and percentage DSM-MDD cases in PGC cohorts

This Table shows the Pearson correlation coefficient (Pearson r) and r^2 (Pearson r2) with P value between PRS prediction Naglekerke's r^2 and percentage of DSM-MDD cases in each PGC cohort, for PRS derived from each P value threshold from GWAS of each definition of depression in UKBiobank. This table contains results from PRS build from GWAS on the full dataset. P values are presented without adjusting for multiple comparisons.

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