Genetic heterogeneity and subtypes of major depression

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ABSTRACT

Background

Major depression (MD) is a heterogeneous disorder; however, the extent to which genetic factors distinguish MD patient subgroups (genetic heterogeneity) remains uncertain. This study sought evidence for genetic heterogeneity in MD.

Methods

Using UK Biobank cohort, the authors defined 16 MD subtypes within eight comparison groups (vegetative symptoms, symptom severity, comorbid anxiety disorder, age at onset, recurrence, suicidality, impairment and postpartum depression; N~3,000-47,000). To compare genetic architecture of these subtypes, subtype-specific genome-wide association studies were performed to estimate SNP-heritability, and genetic correlations within subtype comparison and with other related disorders or traits.

Results

MD subtypes were divergent in their SNP-heritability, and genetic correlations both within subtype comparisons and with other related disorders/traits. Three subtype comparisons (age at onset, suicidality, and impairment) showed significant differences in SNP-heritability; while genetic correlations within subtypes comparisons ranged from 0.55 to 0.86, suggesting genetic profiles are only partially shared among MD subtypes. Furthermore, subtypes that are more clinically challenging, e.g., early-onset, recurrent, suicidal, more severely impaired, had stronger genetic correlations with other psychiatric disorders. MD with atypical features showed a positive genetic correlation (+0.40) with BMI while a negative correlation (-0.09) was found in those with non-atypical symptoms. Novel genomic loci with subtype-specific effects were identified.

Conclusions

These results provide the most comprehensive evidence to date for genetic heterogeneity within MD, and suggest that the phenotypic complexity of MD can be effectively reduced by studying the subtypes which share partially distinct etiologies.

INTRODUCTION

Major depression (MD) is a common psychiatric disorder that affects 15% of the population during lifetime.(1) Individuals with MD vary considerably in symptoms, severity, course, treatment response, and neurobiology.(2) MD heterogeneity is a major research and clinical challenge.(3) Despite major efforts in epidemiological, clinical, and biological psychiatry, this decade-long challenge remains largely unresolved.(4-6) MD subtypes have been proposed within five major categories that focused on: symptoms (typical versus atypical, with or without concomitant anxiety, etc.), etiology (with or without trauma or postpartum exposure), time of onset/time course (early- versus late-onset, recurrent), sex, and treatment outcome (treatment responsive versus resistant).(6) Many of these subtypes, however, exhibit unclear distinctions in underlying biology, psychosocial factors, and treatment efficacy.(6) One of the key biological component is genetics—the extent to which genetic factors distinguish these MD subtypes (i.e. genetic heterogeneity) is largely unknown.

Given its relatively low heritability (30-40%)(7, 8), identifying MD subtypes that are more heritable is of particular importance. Among the proposed subtypes, the sex difference in heritability is the most intensively studied, and current findings support that MD is more heritable in women than in men.(9) Early-onset, recurrent MD, and postpartum depression have been suggested to confer higher genetic liability from family-based studies, which was subsequently confirmed using polygenic risk scores (PRS) in recent MD genome-wide association studies (GWAS).(9-13) Comparisons of MD subtypes between early- versus late-onset, atypical versus non-atypical, with or without adversity have yielded interesting findings (e.g., the genetic overlap with metabolic traits was only found in MD with atypical features subtype, but not among those with non-atypical symptoms).(14) The studies to-date that have used genetic approaches to index the heterogeneity of MD subtypes are encouraging (summarized in ***Table 1***) but overall impeded by a paucity of large cohorts with similar ascertainment, phenotyping, and genotyping.(5) As a result, a systematic comparison across the MD subtypes is lacking and overall evidence for genetic heterogeneity within MD is inconclusive.

The goal of this study was to test genetic heterogeneity in clinically-informed MD subtypes. To accomplish this, we systematically evaluated 16 subtypes in the unique UK Biobank (UKB) cohort with large-scale genomic data and a wide array of phenotypic measures uniformly assessed. In particular, we compared genetic architectures among subtypes by quantifying differences in heritability (*i.e.*, measuring the relative importance of genetic effects on phenotypic variance) and estimating genetic correlations (*i.e.*, to determine if underlying genetic risk factors are identical) within subtype comparisons and with other traits.

METHODS and MATERIALS

To identify MD subtypes and compare their genetic architectures, we carefully selected phenotypes and large-scale genotype data from the UKB. The full protocol and scripts are available via Github.

Participant and phenotype definitions

UKB is a population-based cohort of over 500,000 adults (age 37-73) from across the United Kingdom.(15) UKB has phenotypic data from questionnaires, health records, biological sampling, and physical measurements. Information about mental health including MD was collected using various sources, including touchscreen questionnaires, nurse interviews, hospital admission records, and web-based mental health questionnaires (MHQ) follow-up. The UKB data profile were available elsewhere (15) and briefly described in *Supplementary S1.1*.

MD case definition

Cases were identified using five MD definitions, including (i) lifetime MD based on the Composite International Diagnostic Interview (CIDI) Short Form; (ii) ICD-coded MD based on linked hospital admission records; (iii) Probable MD based on Smith et al.(16); (iv) Self-reported MD as part of past and current medical conditions; and (v) MD cardinal symptoms of anhedonia and dysphoria (*Supplementary table S2.1)*. These MD definitions have been used in previous studies.(17-19) Because some definitions were available only for parts of the UKB samples, to maximize sample size for MD subtypes, we included individuals who met criteria for at least one of the five MD definitions as cases. MD subtypes were all nested in the broad MD group but coming from different MD definitions (*Supplementary table S2.2)*.

MD subtypes

According to major clinical features in MD, we defined 16 MD subtypes within eight comparison dimensions including (i) MD with versus without atypical features based on vegetative symptoms of hypersomnia and weight gain; (ii) severe versus mild/moderate MD based on symptom severity defined in Smith et al.(16) or ICD codes; (iii) MD with or without comorbid anxiety disorder either self-reported or based on ICD codes; (iv) early- versus late-onset MD based on age at which first experienced a ≥2-week episode of cardinal symptoms; (v) recurrent MD vs single-episode MD based on the number of episodes self-reported or ICD codes; (vi) MD with or without suicidal thoughts or self-harm either experienced recently or during the worst episode; (vii) MD with mild, moderate, severe impairment on normal roles; and (viii) postpartum depression (PPD), either self-reported or based on ICD codes (***Table 2***). The majority of these subtypes are included in the five major

categories proposed in the previous meta-review; while the subtypes on suicidality and on impairment—related to general outcomes of MD—are extensions of the category focused on treatment outcomes (*Supplementary S1.1, table S2.3)*.(6)

Control group

We used a common control group without lifetime history of MD to compare with all but the subtypes of comorbid anxiety disorder and PPD. From the entire UKB population, we excluded those with any indications of MD using five MD case criteria described above, and two additional exclusion criteria, help-seeking MD and antidepressant use (medication list in *Supplementary table S2.4*). We further excluded those with ICD-diagnoses of anxiety disorders from the controls for the MD subtype with or without comorbid anxiety disorder. For PPD, we restricted controls to women who reported giving at least one live birth. (*Supplementary table S2.1)*

Exclusionary criteria for cases and controls

We excluded any case or control who met lifetime criteria for schizophrenia, schizoaffective disorder, and bipolar disorder I (including unipolar mania) *(Supplementary table S2.1)*. Thus, anyone who had ICD-diagnosis of schizophrenia/psychosis, bipolar disorder, mania or reported any use of antipsychotics or lithium for psychiatric symptoms (*Supplementary table S2.4*) were excluded from analyses. Application of these criteria removed 2,385 MD cases and 231 controls (*Supplementary figure S3.1)*.

Genotyping, quality control, imputation

Genotype data were available for 488,363 UKB participants, after a stringent quality control procedure and imputation using combined reference panels of Haplotype Reference Consortium (HRC) and UK10K merged with 1000 Genomes phase 3.(15) 459,590 individuals remained after the exclusion of subjects with low-quality genotype data, unmatched ID with phenotype data, consent withdrawal, and non-European ancestry outliers (*Supplementary figure S3.1)*.

Statistical analysis

Genome-wide association studies (GWAS)

We generated GWAS summary statistics for MD subtypes to estimate SNP-heritability and genetic correlations for computational efficiency. In the UKB, about 30% of the participants were found to be related to at least one other person in the cohort up to the 3rd degree.(15) Cryptic relatedness within sample could bias results in GWAS, while restricting to the unrelated individuals would cause a major loss of statistical power. We therefore performed the mixed linear model-based GWAS

analysis (fastGWA) to retain related individuals in the UKB.(20) We first constructed a sparse genetic relationship matrix (GRM) for all included individuals of European ancestries, and then conducted case-control GWAS for each subtype using fastGWA module in GCTA, adjusting for sex, age, and the first 10 PCs(20) (*Supplementary S2.2).*

For subtype-specific GWAS with genome-wide significant SNPs ($p \leq 5x10^{-8}$), we identified independent genomic loci using SNP2GENE module in FUMA(21); then compared our loci with the latest published MD GWAS results which consisted of samples from the Psychiatric Genomics Consortium (PGC), UKB, and 23andMe.(19)

SNP-Heritability

We estimated SNP-heritability (h^2_{SNP}) on the observed scale for each MD subtype using linkage disequilibrium score regression (LDSC).(22) LDSC estimates h^2_{SNP} by regressing GWAS summary statistics on LD scores estimated from a reference population (1000 genomes European samples). To allow comparison between subtypes, we converted the observed h^2_{SNP} to the liability scale, and as previously suggested(23), we corrected for oversampling and extreme phenotyping using sample prevalence, and proportions of the population as cases and controls. Except for PPD, the subtype-specific population prevalence was calculated as MD lifetime prevalence (15%) scaled by the literature-based proportion of subtype in MD, and we used 85% as the proportion of the population as non-MD controls (details in *Supplementary table S2.5*). We provided a figure showing the impact of population case prevalence estimates on h^2_{SNP}. When comparing heritability estimates within subtype comparisons, we cannot directly test for the statistical significance of the difference in estimates due sample overlap; therefore, we considered that estimates are significantly different when non-overlapping confidence intervals are presented.

Genetic correlation

Genetic correlations (r_g) were estimated using High-Definition Likelihood (HDL) method which yields more precise estimates of genetic correlations than LDSC *(Supplementary S2.2)*.(24) We estimated r_g within subtype comparisons using the LD reference computed from 335,265 Genomic British individuals in the UKB.

To examine whether the subtypes differ in their genetic overlap with other psychiatric disorders and traits, we also estimated genetic correlations between these MD subtypes and 11 traits (six psychiatric disorders, neuroticism, self-reported well-being, body mass index, and two cognitive traits) and compared results within subtype comparisons. These disorders and traits were chosen given the strong evidence for their genetic correlations with MD, or in some cases, for their causal

effects on MD.(13, 19) We have used the summary statistics from the latest published GWAS for the calculations of r_g using HDL.(19, 25-34)

Sensitivity analyses

To examine whether our broad MD definition that included less strictly defined cases may bias results, we further restricted the analyses to the CIDI-based definition—previously suggested as the closest to the gold standard for diagnosing MD in the UKB(17, 35, 36)—and performed similar analyses for all subtypes except impairment (*Supplementary S2.2*).

RESULTS

Of 459,590 individuals included in this study (54% females, mean age at recruitment 57 (SD 8.00)), 126,506 (27.53%) met at least one of the five definitions for MD (*i.e.*, broad MD phenotype). After applying exclusion criteria, we retained 124,121 cases and 250,229 controls. Compared with controls, MD cases had more females (64% vs 47%), higher Townsend deprivation index (mean -1.33, SD 3.02 vs -1.63, SD 2.90), more lifetime smokers (57% vs 52%), but did not differ in mean BMI (mean 27.3, SD 4.6 vs 27.3, SD 5.0).

The estimates of SNP-heritability varied across the five MD case definitions, and for the broad MD phenotype it was 7.38% (95% CI= 6.75-8.01%) (*Supplementary figure S3.2*).

Differences in genetic architecture reflect subtype heterogeneity

Overall, SNP-heritability estimates tended to be higher in MD subtypes with more severe manifestation (e.g., MD with atypical features, comorbid anxiety disorder, PPD, severe impairment and severe symptoms subtypes) (***Figure 1a***). All of the subtype comparisons had higher h^2_{SNP} estimates for the more severe manifestation, and three (age at onset, suicidality, and impairment) showed significant differences in h^2_{SNP} estimates (***Figure 1a-b***). All examined genetic correlations within comparisons were significantly less than one and the estimates ranged between 0.55-0.86 (***Figure 1c***).

The h^2_{SNP} estimate for MD with atypical features was the highest among all subtypes, and it was almost twice higher than the estimate for non-atypical MD even though the 95% confidence intervals overlapped (13.35%, CI=7.57-19.13% and 7.48%, CI=6.60-8.36%). The genetic correlation between MD subtype with atypical features and subtype without atypical features was the lowest among all comparisons (r_g=0.55, CI=0.44-0.66) (***Figure 1c***). The two subtypes did not significantly differ in their genetic correlations with PGC MD ***(Figure 2)***; instead major differences were found in their correlations with anorexia nervosa and ADHD. Consistent with previous findings (14, 37, 38), MD

with atypical features showed a strong positive r_g with BMI (0.40, CI=0.34-0.46) while non-atypical MD showed a small negative r_g instead (r_g=-0.09, CI=-0.13 to -0.06). Furthermore, positive correlations with cognitive traits were observed in non-atypical MD (r_g=0.36 and 0.35 with educational attainment and intelligence) which were not found in MD with atypical features (corresponding r_g= 0.04 and 0.07).

The MD subtype with severe symptoms had slightly higher h^2_{SNP} estimate than the one with mild/moderate symptoms, although the two estimates were not significantly different. The r_g within comparison was significantly lower than 1 (0.80, CI=0.68-0.92). However, the two subtypes did not differ in their correlations with other traits except for a stronger r_g with schizophrenia found in the subtype with severe symptoms *(**Figure 1-2**)*.

Assuming the proportions of MD cases with and without comorbid anxiety disorder at 55% and 45%, respectively(39), the former subtype was more heritable than the latter (h^2_{SNP}=11.35%, CI=10.12-12.58%, for MD with comorbid anxiety disorder, compared with 9.43%, CI=7.92-10.95%, for MD without anxiety disorder). The r_g within this comparison was 0.80 (CI=0.73-0.88) (***Figure 1***). Furthermore, the subtype with comorbid anxiety disorder showed higher genetic correlations with MD, schizophrenia and neuroticism, as well as lower correlations with cognitive traits, when compared with the subtype without anxiety disorder (***Figure 2***).

The SNP-heritability of early-onset MD was three times higher than that of the late-onset subtype (9.97%, CI=8.89-11.04% compared with 3.25%, CI=2.46-4.04%). The r_g within comparison was 0.76 (CI=0.68-0.85). (***Figure 1***). Significant differences in their r_g with other traits were observed, including higher genetic correlations in early-onset MD with PGC MD, schizophrenia, anorexia nervosa, and autism spectrum disorder, than in late-onset MD (***Figure 2***).

Recurrent and single-episode MD had similar h^2_{SNP} estimates (7.94% and 7.47%). However, their r_g was significantly lower than one (0.83, CI=0.74-0.92) (***Figure 1***). Compared with single-episode cases, recurrent MD had stronger positive correlations with schizophrenia, bipolar disorder, anorexia nervosa, while lower genetic correlation with BMI (***Figure 2***).

The MD subtype with suicidal thoughts was more heritable than the subtype without (8.14%, CI=7.20-9.07% and 6.25%, CI=5.46-7.03%). The r_g within this comparison was 0.79 (CI=0.73-0.84). The two subtypes in this comparison significantly differed in their genetic correlations with the majority of the other traits considered. Compared with the subtype without suicidal thoughts, the suicidal subtype showed substantially higher positive r_g with PGC MD, schizophrenia, neuroticism, and negative r_g with well-being; while its r_g with cognitive traits was much weaker *(**Figure 1-2**)*.

For subtypes based on impairment, the h^2_{SNP} estimates increased with the degree of impairment, roughly in a dose-response relationship, *i.e.*, mild impairment had the lowest h^2_{SNP} (3.72%, CI=3.09-4.34%), followed by moderate (5.62%, CI=4.81-6.44%) and severe impairment (10.42%, CI=9.08-11.76%). This dose-response relationship was also reflected in the pair-wise genetic correlation estimates, with the r_g comparing mild and severe impairment (0.65, CI=0.58-0.72) markedly lower than the other two correlations (***Figure 1***). We observed a clear trend, that is, the more severe impairment in the subtype, the stronger genetic correlation it had with other psychiatric disorders and neuroticism (positive r_g), and with self-reported well-being (negative r_g), while less severe impairment was more strongly associated with cognitive traits (positive r_g) and with BMI (negative r_g) ***(Figure 2)***.

The h^2_{SNP} of PPD was estimated at 11.31% (CI=6.61-16.0%) which was higher compared with h^2_{SNP} of broad MD phenotype. PPD showed significant positive r_g with other psychiatric disorders, with the strongest r_g observed in PGC MD as expected (0.61, CI=0.53-0.69), and with neuroticism (r_g=0.34) and cognitive traits (r_g=0.35 and 0.41 with educational attainment and intelligence), and a negative r_g with well-being (r_g=-0.39) ***(Figure 2)***.

The broad MD definition was used above to allow sufficient statistical power in analyzing each subtype. We further assessed the impact of MD definition by performing a sensitivity analysis based on more strictly defined MD cases. The SNP heritability of the CIDI-based definition was in line with previously reported (h^2_{SNP}=15.7%, CI=13.4-18.1%, *Supplementary figure S3.2*)(17, 35). Restricting the analyses to the CIDI-based cases, the results were highly similar, except for the comparisons of symptom severity and recurrence, where the CIs of the r_g estimates now included one due to markedly reduced sample sizes in these subtypes (*Supplementary table S2.7*).

Stratified GWAS reveal novel subtype-specific loci

Over all 16 subtype-specific GWAS, we identified 47 genome-wide significant loci (45 non-overlapping) associated with nine subtypes. Less than half (22 loci) were significant in our largest GWAS of broad MD. Comparing with the latest published MD GWAS (19), we found 14 loci that have not been reported on MD, with 3 for early-onset, 3 for recurrent, 3 for suicidal MD, 2 for non-suicidal, 1 for non-atypical symptoms, 1 for moderate impairment and 1 for PPD (***Table 3***; full results on the 45 loci in *Supplementary table S2.6*). The majority (64%) of these 14 loci showed no statistically significant association with the other subtype in comparison (P>0.05; *Supplementary S2.6*), suggesting subtype-specific effects. The chromosome 2 locus for recurrent MD, with the

leading SNP rs6431690, was significant even after the stringent Bonferroni correction (P<3.125*10^{-9}).

DISCUSSION

In this comprehensive report using the large-scale UKB data, we compared the genetic architectures of 16 MD subtypes and demonstrated that these subtypes were divergent in their SNP-heritability and genetic correlations both within subtype comparisons and with other related disorders/traits. Our results provide convincing evidence for genetic heterogeneity within MD, as indexed by its clinical subtypes. These findings suggest that the complexity in the phenotype of MD can be effectively reduced by studying the subtypes which share partially distinct etiologies. In particular, we note the following key findings:

First, clinically-informed subtypes are, in general, genetically more homogeneous than considering all types of MD together. Accurately identifying more homogenous forms is the first step to reduce heterogeneity in MD. The majority of the subtypes showed higher estimates of SNP-heritability compared with MD of all forms. Our results corroborated previous findings from family-based studies that early-onset, recurrent MD and PPD represent more heritable MD subtypes.(10, 12) We further extended the list to include MD with atypical features, MD with or without comorbid anxiety disorder, and with severe impairment. In contrast, subtypes with lower heritability than all-form MD are those with mild/moderate clinical manifestation or with late onset.

Second, we demonstrated subtype heterogeneity in both SNP heritability and genetic correlations. All subtype comparisons showed non-identical genetic sharing (*i.e.*, r_g between subtypes significantly differ from unity) and some had heritability differences (*i.e.*, h^2_{SNP} significantly differ between subtypes). Interestingly, the subtype comparisons on vegetative symptoms, time onset, and impairment showed the strongest evidence for genetic heterogeneity, meaning these clinical features characterize major etiological differences within MD.

However, the observed genetic correlations across subtype comparisons were moderate to high, 0.55-0.86, revealing substantial genetic overlaps between subtypes. The level of genetic correlation can be translated into the proportion of genetic variance in one trait attributable to that of another (r_g^2).(17) Thus, it would suggest about 30-70% of genetic variances are shared within subtype comparisons. In line with previous estimates of genetic correlations between male versus female MD(9) and across MD symptoms(40), our findings confirm that the genetic profiles of MD subtypes are only partially distinct.

The estimates of genetic correlations between subtypes need to be benchmarked against genetic correlations between different psychiatric disorders (e.g., schizophrenia and bipolar disorder, two clinically distinct psychiatric disorders, had a r_g of ~0.70 (28)), between different datasets but with same phenotype (e.g., mean r_g~0.76 across the seven cohorts at PGC MD(13)), and between different populations (e.g., r_g~1 between schizophrenia samples of East Asian and European ancestries(41)). Genetic correlations can be found lower than one due to differences in phenotype definitions, populations, or technical factors(42). In this study, we minimized these potential differences by using the single large sample from UKB. We also restricted the estimation of genetic correlations to within subtype comparisons instead of pair-wise comparisons across all subtypes, to limit the impact of phenotypic differences between subtypes (*e.g.*, we found mean r_g across all subtypes was indeed lower than that within comparison groups). Our genetic correlation estimates are thus reliable for quantifying overall genetic sharing between MD subtypes.

Third, the MD subtypes preserve the overall pattern of genetic sharing found between MD (of all forms) and other psychiatric disorders, but differ in the relationships with other traits. MD was shown to be positively correlated with many psychiatric disorders (e.g., r_g~0.3 with schizophrenia and bipolar disorders) and with BMI (r_g=0.09), and negatively correlated with educational attainment (r_g=-0.13).(13, 19) A similar level of genetic correlations was found between MD subtypes and other psychiatric disorders; notably, we found stronger correlations in the MD subtypes that are more clinically challenging, especially early-onset, recurrent, suicidal, more severely impaired. Regarding their relationships with other traits, MD subtypes showed some differences compared with all MD. The positive correlation found between MD and BMI was only detected in MD with atypical features, but with a markedly higher estimate (r_g~0.5). This result concurred with previous findings mainly using PRS or other samples.(14, 37, 38, 43) In contrast with the negative value found in all MD, we found positive correlations with educational attainment in many MD subtypes. However, this finding might be specific to the UKB cohort as previous research have shown that participation in mental health survey and other optional components is genetically correlated with higher education and intelligence.(44)

Taken together, our findings provide an improved understanding on heritable MD subtypes and overall genetic sharing between subtypes. These results have strong implications in the gene mapping strategies for MD. Current efforts predominantly aim to maximize samples size. The alternative strategy—to reduce phenotypic heterogeneity through more homogeneous phenotype—has not been fully evaluated, potentially due to theoretical and methodological challenges.(45) This strategy relies on the premise that “clinical heterogeneity in MD emerges from an aggregation of

different underlying liabilities expressed through partially distinct biological pathways" (45) which, to the best knowledge, was not proven. Limited by a lack of large-scale dataset with deep phenotyping, prior studies were only able to focus on a few key subtypes.(5, 45) Our comprehensive report, by contrast, convincingly demonstrated genetic heterogeneity in MD, and thus forms a strong theoretical basis for this strategy. We further illustrated the potential of such strategy by performing stratified GWAS on each subtype. This yielded the identification of 47 independent genomic loci, a third of which were undetected in the latest MD GWAS with about 5- to 10-fold more cases than in our subtype-specific analyses. These results warrant further replications in large biobanks with consistent genotyping and phenotyping.

Here we used the UKB data which provide the unique opportunity to evaluate multiple subtypes with sufficient statistical power. We, however, note the following limitations in the context of interpreting the results. First, we were unable to study all MD subtypes, especially the treatment-related subtypes, as more refined clinical and treatment data would be required. We also acknowledge that the quality of phenotypic definitions varied across the subtypes studied, with those relying on self-reported and retrospective recalls of symptoms more compromised than the others. Finally, "healthy volunteer bias" was known for UKB(46) and likely to contribute to part of our results.

Etiological heterogeneity hinders treatment efficacy. Our finding of ubiquitous subtype heterogeneity within MD underscores the potential of drug development and treatment optimization for patient subgroups to achieve precision psychiatry.

URLs:

Full protocol and scripts available via Github: https://github.com/Thuy-Dung-Nguyen/MD-subtypes;

UK Biobank Showcase User Guide (2017): http://biobank.ctsu.ox.ac.uk/crystal/crystal/exinfo/ShowcaseUserGuide.pdf;

UK Biobank-Mental health web-based questionnaire (2017) http://biobank.ctsu.ox.ac.uk/crystal/crystal/docs/mental_health_online.pdf;

GCTA-fastGWA: https://cnsgenomics.com/software/gcta/#fastGWA;

FUMA: https://fuma.ctglab.nl;

LDSC: https://github.com/bulik/ldsc;

HDL: https://github.com/zhenin/HDL;

Howard et al. 2019 MD GWAS summary results: https://datashare.is.ed.ac.uk/handle/10283/3203.

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Disclosures

PFS reports the following potentially competing financial interests. Current: Lundbeck (advisory committee, grant recipient), RBNC Therapeutics (advisory committee, stock ownership). CMB reports: Shire (grant recipient, Scientific Advisory Board member); Idorsia (consultant); Pearson (author, royalty recipient)

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TABLES & FIGURES

Table 1. Summary of current literature on MD subtype heterogeneity

Table 2. MD subtypes and sample sizes

Table 3. 14 genome-wide significant loci from MD subtype-specific GWAS, undetected in the Howard *et al* 2019.

Figure 1. SNP-heritability and pair-wise genetic correlation for MD subtypes.

Figure 2. Genetic correlations between MD subtypes with other psychiatric disorders and related traits

Table 1. Summary of current literature on MD subtype heterogeneity

Subtype category	Clinical features†	Comparisons†	Heritability		Genetic overlap		Subtype specific GWAS
			h^2	h^2_{SNP}	r_g within comparison	Overlap w other traits (PRS/r_g)	
Symptom-based	**Vegetative symptom**	**Atypical**		Null††(14, 37, 43)	0.82 (0.33-1.31)(43)	PRS of metabolic traits more associated with atypical MD(14, 37) r_g atypical w. BMI= 0.53 (95% CI= 0.23-0.82)(43) r_g typical w. BMI= -0.28 (95% CI=-0.55;-0.01)(43)	
		Typical		Null††(14, 37, 43)	0.54 (0.27-0.81)(37)		
	Symptom severity	**Severe** **Mild/ moderate**					
	Comorbid anxiety disorder	**With anxiety** **Without anxiety**					
Time of onset/course	**Age at onset**	**Early**	0.21(0.12-0.28)(10)		0.85 (0.66-0.98)(10)	Stronger PRS association between early-onset MDD with BIP/SCZ(11)	1 locus(11)
		Late	0.23(0.13-0.32)(10)				
	Recurrence	**Single**	0.28(0.14-0.41)(10)		0.86 (0.68-0.97)(10)		2 loci in Han Chinese(47)
		Recurrent	0.41(0.2-0.6)(10)				
Treatment-related & other outcomes	**Suicidality**	**w suicidal thoughts** **w/o suicidal thoughts**					
	Impairment	**Mild** **Moderate** **Severe**					
	PPD	**PPD**	0.44(0.35-0.52)(12)				

Etiologically-based	Environment	With trauma/ adversity		Inconsistent[†††](48, 49)		Stronger association between MD w trauma and body composition, socioeconomic(48)	Not found(49)
		Without trauma/ adversity		Inconsistent [†††](48, 49)	0.77 (0.48-1.05)(48) 0.64 (0.19-1.09)(49)		3 loci in Han Chinese(49)
Gender-based	Sex	Female	0.44(0.25-0.61)(10)	0.22(0.06)(18)	0.89 (0.87-0.91)(9)		Not found(18)
		Male	0.35(0.08-0.63)(10)	0.18(0.06)(18)			1 locus(18)

MD: major depression. PPD: postpartum depression. BIP: Bipolar disorder. SCZ: Schizophrenia. h^2: heritability. h^2_{SNP}: SNP-heritability. r_g: Genetic correlation. PRS: Polygenic Risk Score

[†] The subtypes examined in this study were highlighted in bold. Subtypes with or without trauma were not studied here because similar analyses using the UK biobank were available; and sex-specific subtypes were not studied because it has been heavily studied and evidence were convincing.

[††] Compared with MD with typical symptoms, h^2_g estimates for MD with atypical symptoms was not significantly different in Milaneschi et al. (2016)(14), 0.43 (95% CI=0.04-0.82) vs 0.38 (95% CI=0.05-0.71); in Milaneschi at al. (2017)(43), 0.11 (95% CI=0.05-0.17) vs 0.11 (95% CI=0.07-0.15); and in Badini et al. (2020)(37), 0.14 (95% CI=0.03-0.15) vs 0.12 (95% CI=0.08–0.16).

[†††] Compared with MD without trauma, h2g estimate was higher for MD with trauma in Coleman et al. (2020)(48), 0.12 (95% CI=0.07-0.16) vs 0.12 (95% CI=0.07-0.16), but lower in Peterson et al. (2018)(49), 0.34 (95% CI=0.03-0.65) vs 0.38 (95% CI=0.29-0.47).

Table 2. MD subtypes and sample sizes

Comparison group	Subtype	† Definition	N_{case}	† $N_{control}$
Vegetative symptoms	Atypical symptoms	MD cases who reported both hypersomnia and weight gain	2904	250229
	Non-atypical symptoms	MD cases who did not report both hypersomnia and weight gain	46900	250229
Symptom severity	Severe	Probable recurrent MD (severe) defined by Smith et al.(16); and/or ICD-diagnoses of severe MD (F322, F323, F332, F333)	7923	250229
	Mild/moderate	Probable recurrent MD (moderate) defined by Smith et al.(16), and/or ICD-diagnoses of mild (F320, F330) or moderate depression episode (F321, F331)	11300	250229
Comorbid anxiety disorder	MD with comorbid anxiety, panic attacks, phobia	MD cases with reported social anxiety/phobia, panic attacks, and anxiety, nerves/generalized anxiety disorder, and/or ICD diagnoses of anxiety disorder (F40, F41)	24543	249062
	MD without comorbid anxiety, panic attacks, phobia	MD cases with neither self-reported nor ICD-codes anxiety disorder	16480	249062
Age at onset	Early onset ≤ 30 years old	First 3 octiles of age at which first experiencing a ≥2-week episode of cardinal symptoms	29292	250229
	Late onset ≥ 44 years old	Last 3 octiles of age at which first experiencing a ≥2-week episode of cardinal symptoms	27796	250229
Recurrence	Recurrent episode MD	Probable MD cases with recurrent episodes, and/or with ≥2 episodes of at least two weeks of cardinal symptoms, and/or ICD-diagnosis of recurrent MD (F33)	30219	250229
	Single episode MD	MD cases with one episode of feeling depressed, and/or self-reported a single episode of cardinal symptoms, and/or ICD-diagnosis of non-recurrent MD (F32)	20973	250229
Suicidality	MD with suicidal thoughts	MD cases with reported thoughts of death during worst depression; and/or those with recent thoughts of suicide or self-harm	40976	250229
	MD without suicidal thoughts	MD cases without suicidal thoughts as defined above	37140	250229

Impairment	Mild impairment	Impact of MD on normal roles, including study/employment, childcare and housework, leisure pursuits, during the worst period of depression as 'not at all/a little impact'	28721	250229
	Moderate impairment	Impact of MD is 'somewhat'	28991	250229
	Severe impairment	Impact of MD is 'a lot'	25825	250229
Postpartum	MD related to childbirth	Women who reported post-natal depression during the nurse interview at the baseline recruitment; and/or MD cardinal symptoms related to childbirth; and/or had ICD diagnosis of mental and behavioral disorders associated with the puerperium.	6333	95736

† Method details for deriving subtypes available in *Supplementary table S2.3* and control groups in *Supplementary table S2.1*

Table 3. 14 genome-wide significant loci from MD subtype-specific GWAS, undetected in the Howard *et al* 2019.

Chr	Region	rsID	A1/A2	AF1	Beta	SE	P	Mapped Gene(s)
MD with non-atypical symptoms								
12	113349833-113349833	rs55676265	A/G	0.7869	-0.0063	0.0011	3.40e-08	*OAS1*
Early-onset MD								
7	24548616-24801999	rs2711093	C/T	0.7034	-0.0051	0.0009	1.00e-08	*MPP6, DFNA5*
10	126711107-126738471	rs34260682	G/A	0.9127	0.0080	0.0015	4.51e-08	*CTBP2*
14	60179792-60663420	rs216519	C/A	0.6190	-0.0046	0.0008	2.31e-08	*RTN1, LRRC9, PCNXL4, DHRS7*
Recurrent MD								
2	15311954-15468791	rs6431690	T/C	0.5453	0.0050	0.0008	1.76e-09	*NBAS*
2	212702426-212778384	rs74338595	T/C	0.7086	0.0050	0.0009	2.87e-08	*ERBB4*
19	31891006-31927547	rs2111530	A/G	0.6058	-0.0048	0.0008	1.20e-08	
MD with suicidal thoughts								
1	109873290-110040460	rs11590351	T/C	0.7537	-0.0060	0.0010	8.54e-09	*SORT1, PSMA5, SYPL2, ATXN7L2, CYB561D1, AMIGO1*
4	2412967-2439670	rs113065538	C/A	0.3522	0.0052	0.0009	3.41e-08	*ZFYVE28*
11	90528418-90646073	rs10830592	A/G	0.3213	-0.0054	0.0010	2.43e-08	
MD without suicidal thoughts								
1	239697408-239760514	rs12118109	G/A	0.9589	-0.0121	0.0022	4.68e-08	*CHRM3*
10	76463067-76506933	rs9733673	G/T	0.8500	-0.0075	0.0013	4.68e-09	*ADK*
MD with moderate impairment								
1	243197475-243500994	rs4658548	C/T	0.6282	0.0047	0.0008	1.82e-08	*CEP170, AC092782.1, SDCCAG8*
Postpartum depression								
2	189234143-189682431	rs11683671	C/A	0.9295	-0.0119	0.0021	2.68e-08	*GULP1*

**The Howard et al. (2019) MD GWAS results consisted of samples from the Psychiatric Genomics Consortium, UKB, and 23andMe.(19)*

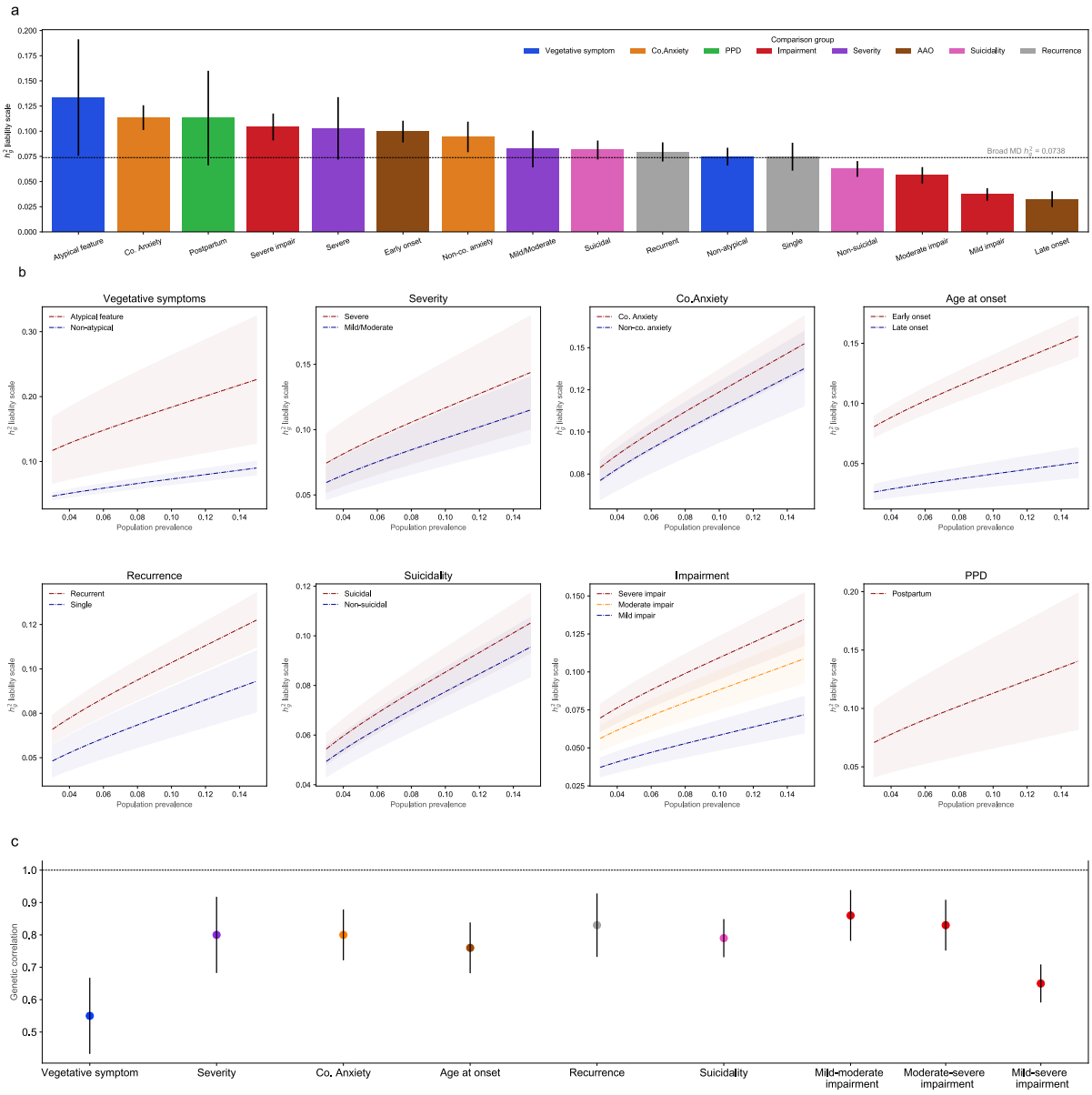

Figure 1. SNP-heritability and pair-wise genetic correlation for MD subtypes. (a) SNP-heritability of MD subtypes on liability scale for each subtype. The bars show point estimates. The error bar shows 95% CI. Same color coding is used for subtypes in the same comparison group. The horizontal line shows SNP-heritability for the broad MD phenotype (h^2_{SNP}=0.74). The sample and population prevalence used for liability-scale conversion available in *Supplementary table S2.5.* **b)** SNP-heritability of MD subtypes on liability-scale for a range of population case prevalence. Each panel shows one comparison group. Shaded areas show 95% CI for SNP-heritability on liability scale. Population control prevalence is fixed for each subtype as in *Supplementary table S2.5.* **(b)** Pair-wise genetic correlation between subtypes within comparison groups. Error bars show 95% CI. *Co-anxiety*: MD with comorbid anxiety; *Non-co. anxiety*: MD without comorbid anxiety. Colors indicate the same comparison group as in (a).

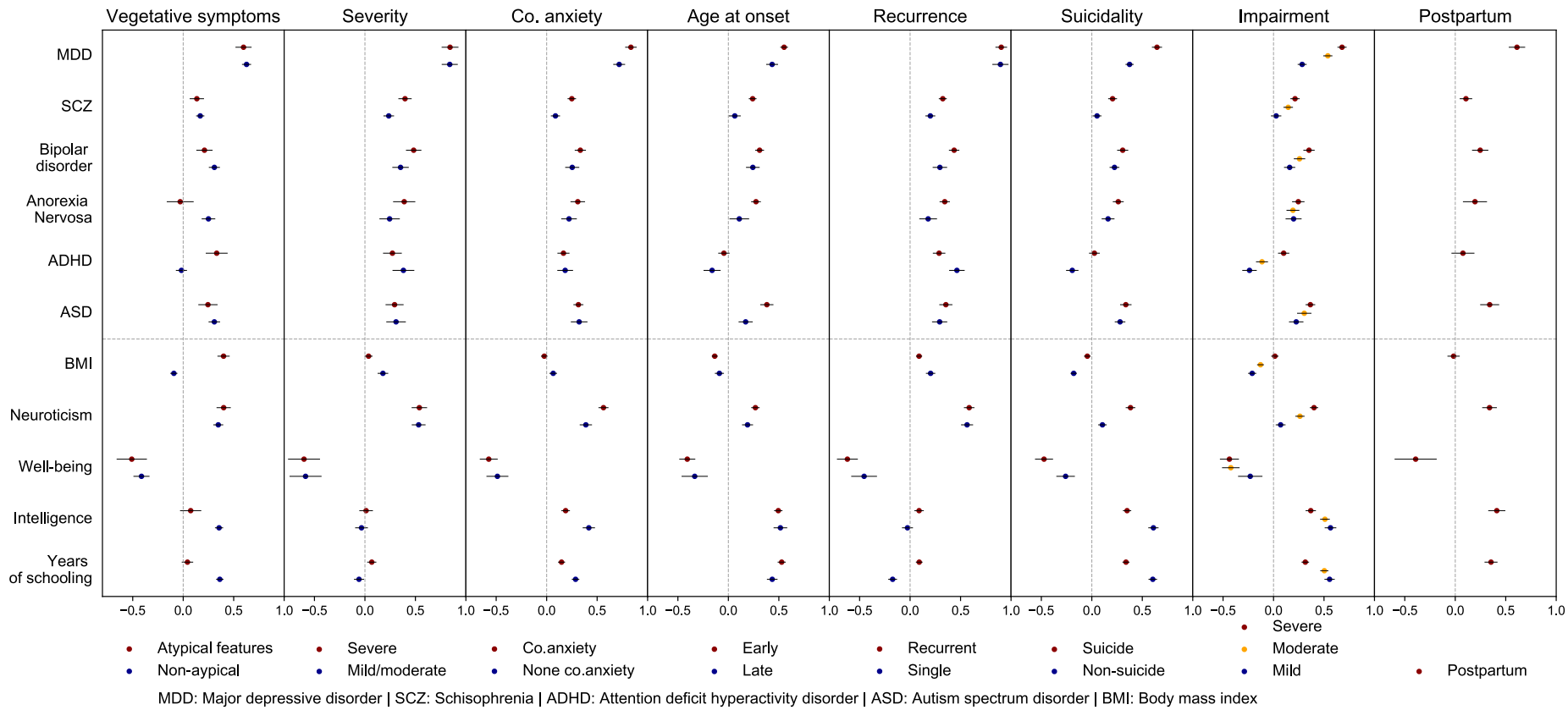

Figure 2. Genetic correlations (r_g) between MD subtypes with other psychiatric disorders and related traits. Each panel shows r_g with other traits for each subtype comparison. r_g with other traits for each subtype are in different colors. Error bars show 95% CI. Vertical dash lines in each panel at r_g=0. Horizontal dash line separates psychiatric and other traits. *Co-anxiety*: MD with comorbid anxiety; *Non-co. anxiety*: MD without comorbid anxiety.