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Additive Genetic Contribution to Symptom Dimensions in Major Depressive Disorder

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Abstract

Major Depressive Disorder is a phenotypically heterogeneous disorder with a complex genetic architecture. In this study, genomic-relatedness-matrix restricted maximum likelihood analysis (GREML) was used to investigate the extent to which variance in depression symptoms/symptom dimensions can be explained by variation in common single nucleotide polymorphisms (SNPs) in a sample of individuals with Major Depressive Disorder (N=1558) who participated in the NIMH Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study. A principal components analysis of items from the Hamilton Rating Scale for Depression (HRSD) obtained prior to treatment revealed four depression symptom components: 1) appetite, 2) core depression symptoms (e.g., depressed mood, anhedonia), 3) insomnia, and 4) anxiety. These symptom dimensions were associated with SNP-based heritability (h^2_{SNP}) estimates of 30%, 14%, 30% and 5%, respectively. Results indicated that the genetic contribution of common SNPs to depression symptom dimensions were not uniform. Appetite and insomnia symptoms in MDD had a relatively strong genetic contribution whereas the genetic contribution was relatively small for core depression and anxiety symptoms. While in need of replication, these results suggest that future gene discovery efforts may strongly benefit from parsing depression into its constituent parts.

Keywords

depression; GREML; genetics; symptom dimensions

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Introduction

Major Depressive Disorder (MDD) is a prevalent and debilitating disorder associated with a tremendous societal burden (Greenberg & Birnbaum, 2005). In recent years research has increasingly focused on elucidating the genetic mechanisms implicated in MDD. Candidate gene and genome wide association studies (GWAS) advanced our understanding of the genetic mechanisms of certain psychiatric disorders (Cichon et al., 2009), but for MDD these methods have not yet achieved their full promise.

GWAS examines hundreds of thousands (or in some cases millions) of single nucleotide polymorphisms (SNPs) to discover single variants with relatively large associations with the phenotypic outcome. Since the effect of individual SNPs on complex diseases is typically small (Manolio et al., 2009) and GWAS carries a substantial multiple testing burden, very large sample sizes are needed to reliably identify candidate polymorphisms via GWAS.

Perhaps as a result of low power, many prior studies have not found replicable associations between MDD and candidate genes (Dunn et al., 2015). Identifying candidate genes that interact with the environment to increase risk for MDD has also been plagued by relatively inconsistent patterns of replication (e.g. Caspi et al., 2003; Fergusson, Horwood, Miller, & Kennedy, 2011) and mixed results from meta-analyses (e.g., Karg, Burmeister, Shedden, & Sen, 2011; Risch et al., 2009)

Even when replicable candidate genes are discovered in MDD, the problem of missing heritability is often observed, as the amount of variance in phenotypic outcomes explained by identified individual genetic variants is small compared to the overall estimated heritability from twin/family studies (Manolio et al., 2009). Various reasons for missing heritability have been suggested, including many different genes contributing a small amount of variance in the phenotype; rare variants that possibly contribute disproportionately to the phenotype; and inadequate power to detect non-additive and epistatic effects of genetic variants (Eichler et al., 2010; Manolio et al., 2009).

Genomic-relatedness-matrix restricted maximum likelihood analysis (GREML) was developed to address the problem of missing heritability in complex diseases by quantifying the relative contribution of single-nucleotide polymorphisms (SNPs), often sampled across the entire genome, to variance in a measured phenotype (i.e., SNP-heritability). GREML estimates genetic resemblance between individuals and then determines the association between this estimate of genetic similarity and variance in a phenotype. The genetic relatedness of unrelated individuals, which indicates the proportion of genes that two individuals have in common, is very small compared to twin pairs (0.00-0.02 for unrelated individuals vs 0.5 or 1.0 for dizygotic or monozygotic twins, respectively); however, this relatedness estimate can quantify how much of the variance in phenotypic outcomes is accounted for by the additive effect of SNPs sampled across the genome (Yang, Lee, Goddard, & Visscher, 2011).

Importantly, GREML cannot provide estimates of heritability due to other non-measured genetic variation. GREML provides an estimate of the added effect of the measured alleles on a given phenotypic outcome (additive genetic effects); however, the heritability estimate

provided by GREML does not include the interaction effects of genes (non-additive genetic effects). Furthermore, GREML heritability estimates in the current study rely on common SNPs, and thus do not include the effects of rare variants, epigenetic processes and other types of genetic polymorphisms. Therefore, GREML can provide an approximate upper-limit estimate of the additive variance in phenotypic outcome that can be explained via GWAS (GREML and GWAS are similarly constrained by measured genetic variation). However, GREML likely provides a lower-limit estimate of the variance in phenotypic outcome that could be explained in a twin study, as genetic similarity in twins captures more genetic variation than typically measured in a SNP-based array.

Differences between heritability estimates obtained from twin studies and GREML may provide important information about the source of missing heritability. For example, if SNP-based heritability estimates from GREML studies are similar to heritability estimates derived from twin studies, we can conclude that the additive effect of common SNPs (and genetic variants that are correlated with those SNPs) explain a large portion of the phenotypic variance. If there is a substantial difference between additive SNP-heritability and twin-based estimates of heritability, this would suggest that other sources of genetic variation also substantially contribute to variation in a phenotype.

GREML was recently used to establish how much variance in various psychiatric outcomes is explained by variation in common SNPs (Palmer et al., 2015; Smoller et al., 2013). Of interest for this study, GREML demonstrated that common SNPs explained 32% of the variance in depression severity (Lubke et al., 2012) and 51% of the variance in age at onset of MDD (Power et al., 2012). Furthermore, common SNPs accounted for 42% of the variance in pharmacological treatment response of patients with MDD (Tansey et al., 2013). Thus, it appears that a large portion of individual differences in depression phenotypes can be accounted for by the additive aggregate contribution of hundreds of thousands of SNPs each contributing a small amount of variance to the depression-related phenotype.

GREML studies of depression to date have generally studied MDD as a single homogenous syndrome, which could limit our understanding of the disorder's genetic architecture. The identification of genetic factors that influence depression is dependent upon how the MDD phenotype is defined, and since only five out of nine DSM-IV/DSM-5 symptoms are needed to meet diagnostic criteria, individuals with MDD have substantial phenotypic heterogeneity. For example, the sample examined here endorsed 1030 unique symptom profiles, with the most common symptom profile only occurring in 1.8% of the sample (Fried & Nesse, 2014). It seems unlikely that these diverse symptom profiles have a common genetic etiology.

As defined by the DSM-5, MDD symptoms span mood, cognitive, and somatic dimensions. Differential heritability of depression symptom dimensions has been reported in twin (Jang, Livesley, Taylor, Stein, & Moon, 2004) and sibling (Korszun et al., 2004) studies. In these studies heritability estimates ranged from 0.00-0.35 across symptom dimensions. Most compellingly, among a large sample of twins, Kendler and colleagues (Kendler, Aggen, & Neale, 2013) recently examined the underlying genetic factors of the DSM-IV criteria for MDD. Instead of a single dimension of genetic liability, three underlying genetic dimensions

were identified that indexed risk for cognitive/psychomotor, mood, and neurovegetative symptoms.

While twin studies suggest that additive genetic effects might differ across depression symptom dimensions, no prior work in depression has examined this question using measured genetic variation (i.e., genome-wide SNPs). In an effort to complement prior work with twins, this study aims to quantify the genetic contribution of common SNPs to depressive symptom dimensions using GREML. Identifying the extent to which common SNPs contribute to these depression phenotypes can help advance our understanding of their etiology and potentially highlight novel symptom clusters for future genetic studies.

In the present study, principal component analysis (PCA) was used to establish symptom dimensions of depression measured by the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960). Symptom dimensions have previously been used in this area (e.g., Jang et al., 2004) but no prior study has examined the SNP-heritability of these dimensions. Although examining the SNP-heritability of symptom dimensions could increase statistical power and measurement reliability compared to examining the heritability of individual items, it is possible that item-specific genetic effects could be obscured within symptom dimensions. To address this possibility, we supplemented symptom dimension analyses by examining the SNP-based heritability of individual HRSD items. Based on the past work reviewed above, we hypothesized that SNP heritability would vary across the depression symptom dimensions.

Methods

Participants

Details about the design of the STAR*D study are available elsewhere (Rush et al., 2004). Participants met DSM-IV criteria for nonpsychotic major depressive disorder at study entry, were 18–75 years of age and were not pregnant or breastfeeding. Exclusion criteria included participants diagnosed with active suicidal ideation or substance use that required acute hospitalization, a primary diagnosis of bipolar, psychotic obsessive-compulsive and/or eating disorders, those with general medical conditions that precluded protocol medications and those who had shown nonresponse or intolerance to protocol medications within the current depressive episode prior to study enrollment.

DNA samples were obtained from 1953 participants from the 4,041 treatment seeking individuals enrolled in the STAR*D study. There were slight differences between the participants who provided DNA samples and participants who did not. Genotyped participants were older, better educated, had higher household incomes and were more likely to be retired or married, however HRSD scores did not significantly differ between groups (for more details, see McMahon et al., 2006). The present analyses focused on individuals of European ancestry identified via genomic principal component analyses (see Table 1 for sociodemographic and clinical characteristics of the samples).

Measures

Genotyping, Quality Control, and Genetic Principal Component Analysis— Participants in STAR*D were genotyped on the Affymetrix Genome-wide Human SNP Array 5.0 that provided genotypes on 500,453 markers. Quality control (QC) of the genotyped SNPs was completed using SNP & Variation Suite v7.7.3 (Golden Helix, Inc., Bozeman, MT, www.goldenhelix.com). Inclusion criteria for markers were: minor allele frequency > 1%, Hardy Weinberg equilibrium p-value > 1E-4, and genotyping call rate ≥ 98%. Gender check indicated that for 29 individuals genetically-based gender was inconsistent with the interview assessment of gender, these individuals were re-classified to be consistent with genetically-based gender.

The present analyses focused on a subset of individuals of European ancestry identified via genomic principal component analyses (PCA). Participants who were more than two standard deviations away from the mean on the first ancestral component that distinguished subjects of European and African ancestry were excluded from the current analysis. PCA reduced the sample from a mixed population of 1948 individuals to a more homogeneous population of 1618 subjects of European ancestry. Application of the genotyping QC criteria to the 1618 subject identified 357,589 markers (350,037 autosomal SNPs) from 1617 individuals (one individual was removed due to a low genotyping rate). A second set of analysis was conducted in a sample of individuals no more related than cousins two to three times removed (the unrelated sample; N=1361; see supplementary materials).

Hamilton Rating Scale for Depression—Depression severity at study enrollment prior to trial treatment initiation was measured with the HRSD (Hamilton, 1960). The HRSD is a clinician administered semi-structured interview consisting of 17 items. Items have 3 to 5 possible rating options that increase in severity, with total scores ranging from 0 to 50. The HRSD has demonstrated good reliability and validity (Knesevich, Biggs, Clayton, & Ziegler, 1977; Trajković et al., 2011). Composite scores resulting from a principal components analysis (described below) were used for study analyses.

Analysis

Phenotypic Principal Component Analysis—The primary aims of the study were achieved by using restricted maximum likelihood analysis principal component analysis (PCA) to identify the most prominent depression symptom dimensions. Phenotypic reduction (using varimax rotation) of the 17 HRSD items was conducted in SAS version 9.4 (SAS Institute Inc, Cary, NC) to identify the minimum number of orthogonal dimensions that explain the variance across the items. Prior to analysis, each item was normalized (M=0, SD=1) to ensure metric consistency across items.

PCA was executed using an iterative process where the analysis was repeated each time an item was removed if it failed to meet the loading criteria (>0.40) on at least one component or met the loading criteria on more than one component (i.e. a complex loading item). The number of components to be retained was based on several criteria: (a) examinations of the observed eigenvalues and comparison to parallel analysis-based (PA) eigenvalues from 100 randomly generated datasets of similar size, (b) consistency with findings from the previous

meta-analysis of the HRSD (Shafer, 2006), and (c) consistency of the loading patterns. Once the number of components was determined, composite scores based on the sum of items identified for each component in the PCA were constructed for use in genetic analyses. Models (described below) were conducted on the final set of participants who had both genetic and phenotypic data (N=1558 for analyses using all subjects of European ancestry; N=1345 for analyses using a subsample of unrelated individuals of European ancestry).

Genomic Relatedness Maximum Likelihood Analyses—Genetic relationship matrices were derived using all of the SNPs that survived QC (N=350,037). Models (described below) were conducted on both the full and unrelated sample. The unrelated sample controls for the effects of cryptic relatedness, which could artificially inflate heritability estimates. Five models were conducted on each phenotype to fully describe the effects of covariates. Covariates were age, genetically-determined gender, and the first three ancestral principal components (APCs). APCs were included as covariates as a control for residual genomic stratification and batch (e.g., laboratory conditions, reagent lots and personnel differences) effects (Leek et al., 2010).

Results

Phenotypic Principal Component Analysis

Comparison of the observed eigenvalues to eigenvalues from the parallel analyses suggested that five components were sufficient (Supplemental Figure 1). Therefore, results from four-, five-, and six-component solutions were compared. Comparison of the loading patterns across the models were fairly consistent, producing similar components that have been previously reported (Supplemental Table 1) (Shafer, 2006).

In the four-component solution, the first component, which we labeled core depression, consisted of six items and measured depressed mood, guilt, suicide, anhedonia, somatic energy, and psychomotor retardation. The second component, which we labeled anxiety, was indicated by four items measuring psychological anxiety, somatic anxiety, hypochondriasis, and psychomotor agitation. The third component, which we labeled appetite, was indicated by two items measuring appetite and weight loss. Finally, the fourth component, which we labeled insomnia, was indicated by items measuring initial insomnia, middle insomnia, and delayed insomnia. This four-component solution was consistent with previous analyses of the HRSD factor structure (Shafer, 2006).

The five- and six-component solutions were slightly less consistent with the previous literature. In the five-component solution, insight formed its own component with psychomotor retardation. In the six-component solution, anhedonia and somatic energy formed the fifth component while insight and psychomotor retardation formed the sixth component. Libido dropped out of both the five- and six-component solutions.

Based on these findings, a final four-component solution, with libido and insight removed, was favored due to its consistency with previous research and clearer interpretability of loadings. The first four eigenvalues from the four-component solution were 2.32, 1.59, 1.37, and 1.21 (see Table 2 for PCA loadings). These components accounted for 43% of the

variance. Consequently, our GREML analysis described below focused on sum scores of items based on this four-component solution.

Additive Effects of Autosomal SNPs on Depression Symptoms and Symptom Dimensions

Table 3 summarizes the results for the four depression symptom dimensions using the full sample; similar results were observed in the unrelated sample (Supplementary Table 2). Results from the likelihood ratio tests comparing the observed h^2_{SNP} estimates to a model with no effect indicated that many of the h^2_{SNP} estimates were significant. The unadjusted h^2_{SNP} (standard error; SE) for appetite, core depression, insomnia, and anxiety dimensions were 0.30 (0.16), 0.14 (0.13), 0.30 (0.13), and 0.05 (0.11). Controlling for age, gender, or population stratification had minimal effects on the observed estimates, especially for the insomnia and appetite dimensions.

Table 4 summarizes the results for the individual HRSD items using the full sample; similar results were observed for each HRSD item in the unrelated sample (Supplementary Table 3). There was significant consistency between h^2_{SNP} estimates reported for depression symptom dimensions and the individual items that were included in those symptoms dimensions. Specifically, 13 out of 15 individual items fell within two standard errors of the mean of their respective dimension. The exceptions were psychomotor retardation (on the core depression dimension) and psychological anxiety (on the anxiety dimension), which had larger h^2_{SNP} estimates than would be expected given the h^2_{SNP} estimates of their dimensions.

Discussion

GREML was used to estimate the SNP-based heritability of symptom severity across four depression symptom dimensions obtained from principal components analysis of the HRSD. There was moderate and variable SNP unadjusted heritability estimates across the four depression dimensions: h^2_{SNP} ranged from .14 to .30 (see Table 3). SNP heritability was statistically significant for three of the four symptom dimensions ($p = .11$ for the anxiety dimension).

In analyses that included covariates (i.e., age, gender, ancestry related principal components to account for potential population stratification), only the appetite and insomnia symptoms retained significant SNP heritability estimates. Thus, although in some analyses most depression dimensions had a significant h^2_{SNP}, heritability estimates appeared to be most robust for insomnia and appetite symptoms. Further, the h^2_{SNP} of individual HRSD items significantly overlapped with the h^2_{SNP} of their respective symptom dimensions. Nevertheless, these findings should be interpreted with caution due to the relatively large standard errors observed.

Comparing findings across studies is complex because depression assessments typically vary as do sample characteristics. Even so, when comparing the current findings to results from twin studies (Jang et al., 2004; Kendler, Aggen, & Neale, 2013; Kendler et al., 1995), heritability estimates for core depression and anxiety symptom dimensions appear smaller in our study than in prior work with twins. Smaller heritability estimates compared to twin

studies are expected since GREML only utilizes common SNPs. As such, there is a difference in the estimation of additive genetic effects, since our method only captures the contribution from causal variants in linkage disequilibrium with the genotyped SNPs. In contrast, twin studies reflect genetic variance from the entire allele frequency spectrum (common and rare; SNPs and various types of genetic polymorphisms).

Another consideration is that individuals in the current sample were all diagnosed with MDD, which very likely restricted the range of core depression symptom severity in the current sample (i.e., sad mood or anhedonia is required for a diagnosis of MDD). Indeed, sad mood was by far the most commonly endorsed symptom in this sample (Fried & Nesse, 2014). Restricted range may have been less of an issue for most other symptom dimensions, as participants could have a variety of different combinations of other symptoms and still meet criteria for MDD. Interestingly, the heritability estimates for insomnia and appetite symptom dimensions were roughly equivalent to those reported in twin studies.

The STAR*D cohort is one of the few samples of MDD patients large enough to sufficiently power GREML analyses, however sample characteristics might limit inferences drawn from these findings. The sample consisted of treatment-seeking individuals, who presented with significant psychiatric comorbidity. There is evidence that treatment-seeking and comorbidity influence depression symptom profiles (Galbaud du Fort, Newman, Boothroyd, & Bland, 1999), which might influence the generalizability of heritability estimates. Participants also endorsed a chronic symptom course, which might have influenced heritability estimates since severe and recurrent depression predict familial aggregation (Sullivan, Neale, & Kendler, 2000). As is typical for clinical trials, STAR*D excluded actively suicidal patients. This likely restricted the range of severity scores for this symptom, and therefore could have influenced the heritability estimate for this symptom and the symptom dimension in which it is included (core depression). The reported heritability estimates are based on a sample diagnosed with MDD, and it is unclear if these results generalize to depression symptoms that are present in unselected samples. However, these findings can guide research in subclinical samples, since subclinical depression and depression are likely on a continuum, with subclinical depression being more common among family members of individuals diagnosed with MDD (Sherbourne et al., 1994). Furthermore, there is evidence suggesting that heritability estimates of depression symptoms are similar in MDD samples and the general population (Jang et al., 2004). This study thus provides a framework for subsequent work (i.e., studying symptom dimensions), but replication of these findings in non-treatment seeking and unselected samples is needed.

The current findings highlight the importance of examining the aggregate contribution of common genetic variation indexed on GWAS arrays to different facets of complex phenotypes, such as depression, especially as it is apparent that hundreds of thousands of case-control subjects are needed to agnostically examine the genetic contribution of individual genetic variants to complex traits using traditional GWAS. Notably, findings from the current study only extend to subjects of similar ancestral background and causal variants that are in linkage disequilibrium with the common (MAF > 1%) genotyped SNPs and do not capture effects of rare variants or other unmeasured genetic variation. Likewise, the

GREML approach estimates the narrow-sense SNP-heritability of traits and provides no indication of non-additive genetic effects.

Although these findings add to a growing body of evidence suggesting that depression symptom dimensions are differentially heritable (Jang et al., 2004; Kendler et al., 2013), this work cannot disentangle whether genetic variation contributes to heterogeneity in the etiology of depression and/or whether there is a common etiology and genetic variation contributes to heterogeneity in the phenotypic presentation of depression. This will be an important direction for future research. Similarly, an important future extension will be to estimate the genetic overlap for the depression dimensions. For instance, does similar genetic variation contribute to the appetite and insomnia symptoms versus the depression and anxiety symptoms in MDD, and is there genetic variation that contributes to all symptoms? The current study was underpowered to test this assumption; however, combining the results of a study examining the genetic overlap of depression symptom dimensions with the current findings will help to further understand the genetic architecture of depression symptom dimensions.

To our knowledge this is the first study to use GREML to examine the SNP-based heritability of depression symptom dimensions. Findings indicate that these depression symptom dimensions have differential SNP-based heritability among individuals diagnosed with MDD. Specifically, core depression (e.g., sad mood, anhedonia, guilt) and anxiety symptom dimensions had relatively low SNP heritability (14% and 5%, respectively) whereas insomnia and appetite dimensions had relatively larger SNP heritability (30% for both).

These findings emphasize the importance of considering the heterogeneous symptom dimensions that constitute MDD, particularly for researchers studying the genetic etiology of MDD. Symptom dimensions with a stronger putative genetic etiology may be more promising candidates for gene discovery efforts than symptom dimensions with relatively little evidence of genetic etiology. Furthermore, these results suggest that for the appetite and insomnia dimensions, where SNP-based heritability estimates are similar to heritability estimates derived from twin studies, adequately powered GWAS of common SNPs should be able to explain a significant portion of the genetic variance. For the anxiety and core depression dimensions, where SNP-based heritability estimates are lower than those reported in twin studies, other sources of genetic variance (e.g., rare variants, epistasis, epigenetic processes) might need to be investigated to uncover the missing heritability. Examining the heritability of symptom dimensions that cross traditional DSM-5 diagnoses is also an important future direction (Insel et al., 2010), particularly given recent evidence that diagnostically distinct disorders partially share a common genetic etiology (Smoller et al., 2013). Taken together, future research should consider symptom heterogeneity when studying underlying causes of depression-related phenomena, as etiological factors may differentially influence symptom dimensions in complex phenotypes such as depression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Data and biomaterials were obtained from the limited access datasets distributed from the NIH-supported "Sequenced Treatment Alternatives to Relieve Depression" (STAR*D). STAR*D focused on non-psychotic major depressive disorder in adults seen in outpatient settings. The primary purpose of this research study was to determine which treatments work best if the first treatment with medication does not produce an acceptable response. The study was supported by NIMH Contract # N01MH90003 to the University of Texas Southwestern Medical Center. The ClinicalTrials.gov identifier is NCT00021528. Dr. Rohan Palmer is supported by K01AA021113 from the National Institute on Alcohol Abuse and Alcoholism (NIAAA). The contents of this manuscript do not represent the views of the National Institutes of Health, the Department of Veterans Affairs, or the United States Government.

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General Scientific Summary

The genetic underpinnings of MDD remain enigmatic despite significant research efforts. This study suggests that depression symptom dimensions might have different heritability estimates, and that future genetic research might benefit from parsing depression into its constituent parts.

Table 1

Demographic and clinical characteristics of the samples

	Full Sample (N=1558)	Unrelated Sample (N=1345)
Sociodemographic:		
Age	43 (13.5)	43.1 (13.6)
Female	60.9%	58.6%
Education in years	13.7 (3.4)	14.1 (3)
Married	37.8%	37.8%
Clinical:		
Age of first depressive episode	25.5 (14.9)	25 (14.7)
Number of depressive episodes	4.2 (10.4)	4.3 (10.4)
Months in current episode	23.9 (52.3)	22.3 (48.6)
Axis I comorbidity present	45.4%	46.3%
Axis II comorbidity present	54.9%	56.3%
HRSD score	22.3 (4.9)	22.7 (5.1)

Table 2

Component loadings of each HRSD item on the four components

	Component			
HRSD Variable	**1**	**2**	**3**	**4**
Initial Insomnia	0.054	0.097	0.067	0.602
Middle Insomnia	0.074	0.003	−0.031	0.765
Delayed Insomnia	−0.044	0.080	0.104	0.656
Depressed Mood	0.534	0.134	0.173	0.187
Psychological Anxiety	0.202	0.676	0.057	0.015
Insight	-	-	-	-
Appetite	0.089	0.044	0.859	0.093
Weight Loss	0.004	0.039	0.872	0.059
Somatic Anxiety	0.195	0.713	0.043	0.063
Hypochondriasis	0.055	0.500	−0.124	0.009
Guilt	0.460	0.080	0.033	−0.177
Suicide	0.473	0.143	0.086	−0.083
Work and Interests	0.609	0.012	0.006	−0.032
Somatic Energy	0.533	−0.004	−0.124	0.024
Psychomotor Retardation	0.458	−0.110	0.052	0.074
Psychomotor Agitation	−0.065	0.518	0.088	0.185
Libido	-	-	-	-

Table showing component loadings (i.e., correlations between each variable and the component).

Table 3

SNP heritability (h^2_{SNP}) of HRSD depression sub-scales (full sample, N=1558)

Model	N	h^2_{SNP}	(*SE*)	P
No Covariates				
Somatic	1558	0.296	0.159	0.035
Depression	1558	0.143	0.132	0.036
Insomnia	1558	0.303	0.134	<0.001
Anxiety	1558	0.047	0.068	0.109
Age as covariate				
Somatic	1558	0.321	0.160	0.025
Depression	1558	0.147	0.133	0.033
Insomnia	1558	0.277	0.130	<0.001
Anxiety	1558	0.049	0.070	0.105
Gender as covariate				
Somatic	1558	0.296	0.159	0.035
Depression	1558	0.143	0.133	0.037
Insomnia	1558	0.303	0.134	<0.001
Anxiety	1558	0.048	0.069	0.108
APCs as covariate				
Somatic	1558	0.359	0.163	0.010
Depression	1558	0.127	0.165	0.214
Insomnia	1558	0.241	0.152	0.035
Anxiety	1558	<0.001	0.163	0.500
Age, Gender, APCs as covariates				
Somatic	1558	0.336	0.163	0.014
Depression	1558	0.127	0.165	0.214
Insomnia	1558	0.211	0.151	0.054
Anxiety	1558	<0.001	0.164	0.500

Abbreviations: P - p-value form the one-tailed t-tests; SE - standard error of the estimate

Table 4

SNP heritability (h^2_{SNP}) of HRSD items (full sample, N=1558)

Model	N	h^2_{SNP}	(*SE*)	P
No Covariates				
Initial Insomnia	1558	0.22	0.12	<0.01
Middle Insomnia	1558	0.06	0.11	0.19
Delayed Insomnia	1558	0.18	0.12	<0.01
Depressed Mood	1558	0.04	0.09	0.27
Guilt	1558	0.06	0.09	0.10
Suicide	1558	0.03	0.05	0.21
Work and Interest	1558	0.36	0.14	<0.01
Somatic Energy	1558	0.20	0.16	0.16
Psychomotor Retardation	1558	0.53	0.15	<0.01
Psychological Anxiety	1558	0.34	0.16	0.01
Somatic Anxiety	1558	0.02	0.07	0.40
Hypochondriasis	1558	0.12	0.07	<0.01
Psychomotor Agitation	1558	0.10	0.13	0.17
Appetite	1558	0.43	0.16	0.01
Weight Loss	1558	0.10	0.13	0.13
Insight	1558	0.06	0.09	0.10
Libido	1558	0.29	0.16	0.06
Age, Gender, APCs as covariates				
Initial Insomnia	1558	0.13	0.16	0.17
Middle Insomnia	1558	0.06	0.15	0.32
Delayed Insomnia	1558	<0.01	0.15	0.50
Depressed Mood	1558	0.05	0.18	0.41
Guilt	1558	<0.01	0.17	0.50
Suicide	1558	<0.01	0.17	0.50
Work and Interest	1558	0.29	0.16	0.03
Somatic Energy	1558	0.27	0.17	0.05
Psychomotor Retardation	1558	0.57	0.16	<0.01
Psychological Anxiety	1558	0.37	0.17	0.01
Somatic Anxiety	1558	<0.01	0.16	0.50
Hypochondriasis	1558	<0.01	0.17	0.50
Psychomotor Agitation	1558	0.12	0.16	0.22
Appetite	1558	0.49	0.16	<0.01
Weight Loss	1558	0.12	0.16	0.22
Insight	1558	<0.01	0.17	0.50
Libido	1558	0.36	0.17	0.02

Abbreviations: P - p-value form the one-tailed t-tests; SE - standard error of the estimate