RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART B
Neuropsychiatric Genetics

Genome-Wide Association Study of Generalized Anxiety Symptoms in the Hispanic Community Health Study/Study of Latinos

Erin C. Dunn,[1,2,3]* Tamar Sofer,[4] Linda C. Gallo,[5] Stephanie M. Gogarten,[4] Kathleen F. Kerr,[4] Chia-Yen Chen,[1,2,3,6] Murray B. Stein,[7] Robert J. Ursano,[8] Xiuqing Guo,[9] Yucheng Jia,[9] Qibin Qi,[10] Jerome I. Rotter,[9,11] Maria Argos,[12] Jianwen Cai,[13] Frank J. Penedo,[14] Krista Perreira,[15] Sylvia Wassertheil-Smoller,[10] and Jordan W. Smoller[1,2,3]

[1]Psychiatric and Neurodevelopmental Genetics Unit, Massachusetts General Hospital, Boston, Massachusetts

[2]Department of Psychiatry, Harvard Medical School, Boston, Massachusetts

[3]Stanley Center for Psychiatric Research, The Broad Institute of Harvard and MIT, Cambridge, Massachusetts

[4]Department of Biostatistics, University of Washington, Seattle, Washington

[5]Department of Psychology, San Diego State University, La Jolla, California

[6]Analytic and Translational Genetics Unit, Massachusetts General Hospital, Boston, Massachusetts

[7]Department of Psychiatry, University of California San Diego, San Diego, California

[8]Department of Psychiatry, Uniformed Services University of the Health Sciences, Bethesda, Maryland

[9]Department of Pediatrics, Institute for Translational Genomics and Population Sciences, Los Angeles Biomedical Research Institute, Harbor-UCLA Medical Center, Torrance, California

[10]Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, New York

[11]Department of Medicine, Institute for Translational Genomics and Population Sciences, Los Angeles Biomedical Research Institute, Harbor-UCLA Medical Center, Torrance, California

[12]School of Public Health, University of Illinois at Chicago, Chicago, Illinois

[13]Department of Biostatistics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

[14]Department of Medical Social Sciences, Northwestern University, Chicago, Illinois

[15]College and Arts and Sciences, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

Manuscript Received: 9 December 2015; Manuscript Accepted: 14 March 2016

Although generalized anxiety disorder (GAD) is heritable and aggregates in families, no genomic loci associated with GAD have been reported. We aimed to discover potential loci by conducting a genome-wide analysis of GAD symptoms in a large, population-based sample of Hispanic/Latino adults. Data came from 12,282 participants (aged 18–74) in the Hispanic Community Health Study/Study of Latinos. Using a shortened Spielberger Trait Anxiety measure, we analyzed the following: (i) a GAD symptoms score restricted to the three items tapping diagnostic features of GAD as defined by DSM-V; and (ii) a total trait anxiety score based on summing responses to all ten items. We first calculated the heritability due to common variants (h^2_{SNP}) and then conducted a genome-wide association study (GWAS) of GAD symptoms. Replication was attempted in three independent Hispanic cohorts (Multi-Ethnic Study of Atherosclerosis, Women's Health Initiative, Army STARRS). The GAD symptoms score showed evidence of modest heritability (7.2%; $P = 0.03$), while the total trait anxiety score did not (4.97%; $P = 0.20$). One genotyped SNP (rs78602344) intronic to thrombospondin 2 (*THBS2*) was

Disclosure: Dr. Dunn takes responsibility for the integrity of the data and accuracy of the analyses. All authors have reviewed and approved the final manuscript. None of the authors have any financial or other conflicts of interest.

Grant sponsor: National Heart, Lung, and Blood Institute (NHLBI); Grant numbers: N01- HC65233, N01-HC65234, N01-HC65235, N01-HC65236, N01-HC65237; Grant sponsor: National Institute of Mental Health of the National Institutes of Health; Grant number: K01MH102403; Grant sponsor: NARSAD Young Investigator Grant from the Brain & Behavior Research Foundation.

*Correspondence to:
Erin C. Dunn, Sc.D., M.P.H., Psychiatric and Neurodevelopmental Genetics Unit, Center for Human Genetic Research, Massachusetts General Hospital, 185 Cambridge Street, Simches Research Building 6th Floor, Boston, MA 02114.
E-mail: edunn2@mgh.harvard.edu

Article first published online in Wiley Online Library (wileyonlinelibrary.com): 9 May 2016
DOI 10.1002/ajmg.b.32448

nominally associated ($P = 5.28 \times 10^{-8}$) in the primary analysis adjusting for psychiatric medication use and significantly associated with the GAD symptoms score in the analysis excluding medication users ($P = 4.18 \times 10^{-8}$). However, meta-analysis of the replication samples did not support this association. Although we identified a genome-wide significant locus in this sample, we were unable to replicate this finding. Evidence for heritability was also only detected for GAD symptoms, and not the trait anxiety measure, suggesting differential genetic influences within the domain of trait anxiety.

Key words: genetic association study; anxiety; Hispanics/Latinos

How to Cite this Article:
Dunn EC, Sofer T, Gallo LC, Gogarten SM, Kerr KF, Chen C-Y, Stein MB, Ursano RJ, Guo X, Jia Y, Qi Q, Rotter JI, Argos M, Cai J, Penedo FJ, Perreira K, Wassertheil-Smoller S, Smoller JW. 2017. Genome-Wide Association Study of Generalized Anxiety Symptoms in the Hispanic Community Health Study/Study of Latinos.
Am J Med Genet Part B 174B:132–143.

INTRODUCTION

Generalized anxiety disorder (GAD) is a mental disorder characterized by persistent uncontrollable worry and symptoms of arousal (e.g., restlessness, insomnia, muscle tension, irritability) [Hoge et al., 2012; American Psychiatric Association, 2013; Stein and Sareen, 2015]. GAD is common in the United States and worldwide [Grant et al., 2005; Kessler et al., 2005a,b; Wittchen and Jacobi, 2005; Wittchen et al., 2011]. Retrospective epidemiological studies suggest the past year prevalence of GAD is 3.1% and lifetime prevalence is 5.7% [Kessler et al., 2005a,b]. Even higher estimates have been observed from prospective studies (14.2% lifetime; 4.2% past year) [Moffitt et al., 2010]. Though GAD is about half as common in Hispanics/Latinos compared to Whites [Grant et al., 2005; Asnaani et al., 2010], Hispanics/Latinos represent one of the fastest growing populations in the United States [Passel et al., 2011; Brown, 2014, June 26], making the population burden of GAD in the United States, therefore, quite large. GAD is also a highly comorbid disorder, with about 90% of people with GAD experiencing at least one other DSM-IV Axis 1 or Axis 2 disorder [Grant et al., 2005]. Given its prevalence and profound social and economic costs [Hoffman et al., 2008; Newman et al., 2013], it is of strong interest to identify factors associated with the development of GAD.

Exploration of the role of genetic factors in the etiology of GAD is warranted as GAD appears attributable, in part, to genetic variation [Shimada-Sugimoto et al., 2015]. Family studies have found first degree relatives of people with GAD have six times the odds of having GAD compared to first degree relatives of those without GAD [Hettema et al., 2001]. Twin studies also suggest GAD is moderately heritable, with 32% of the variation in the population risk of GAD being attributable to genetic variation [Hettema et al., 2001]. Despite evidence of family aggregation, there have not yet been any published genome-wide association studies (GWAS) of GAD or GAD symptoms. Given the recent pursuit of GWAS for other anxiety disorders, notably post-traumatic stress disorder [Guffanti et al., 2013; Logue et al., 2013; Xie et al., 2013] and panic disorder [Otowa et al., 2009 2010; Erhardt et al., 2011], as well as efforts to examine domains related to GAD, including anxiety sensitivity [Davies et al., 2015], or composite indicators of anxiety disorder [Otowa et al., 2014], we sought to identify genomic loci linked to GAD by conducting a genome-wide analysis of GAD symptoms. We used a dimensional measure of trait anxiety symptoms chosen to match DSM-5 criteria for GAD. Use of a dimensional measure enables an examination of the full range of quantitative variation, rather than extremes in this quantitative distribution (e.g., cases versus controls) and may be a statistically more powerful approach to identify variants associated with GAD [Plomin et al., 2009].

In this report, we present results from the first GWAS of GAD symptoms, where we found a genome-wide significant association between a SNP intronic to thrombospondin 2 (*THBS2*) and GAD symptoms in a large, diverse, and population-based sample of Hispanic/Latino adults. This finding did not replicate in a meta-analysis of three independent samples of Hispanic/Latino adults. We also present results from a SNP-chip heritability analysis, where we found evidence of modest heritability in GAD symptoms (7.2%), but no statistically significant heritability for a broader measure of trait anxiety symptoms.

MATERIALS AND METHODS

Overview

The Hispanic Community Health Study/Study of Latinos (HCHS/SOL) is a community-based prospective cohort study following 16,415 self-identified Hispanic/Latino adults (aged 18–74 at screening) and was designed to examine the distribution and determinants of chronic health conditions, including diabetes, pulmonary disease, and cardiovascular disease. As described elsewhere [Lavange et al., 2010], participants were recruited via a stratified two-stage area probability sample of households across four cities in the United States (Chicago, IL; Miami, FL; Bronx, NY; San Diego, CA). The majority of the sample self-identified with the following background groups: Central American (n = 1,730), Cuban (n = 2,348), Dominican (n = 1,460), Mexican (n = 6,471), Puerto Rican (n = 2,728), and South American (n = 1,068). Baseline examinations were conducted between 2008 and 2011. Institutional Review Boards at each field center approved the study and all participants provided written informed consent. In the current study, we analyzed data from 12,254 respondents who consented to provide blood for the purpose of genotyping and had complete outcome and relevant covariates information (to be described

later), as well as non-missing records of antianxiety and antidepressants medication use.

Phenotype Definition

Anxiety symptoms were assessed at baseline using a 10-item Spielberger State-Trait Anxiety Inventory (STAI-T) administered in the participant's preferred language (Spanish or English) [Bromberger and Matthews, 1996; Bergua et al., 2015]. This a short form version of the 20 item STAI-T [Spielberger, 1989), which is a valid and commonly used measure of trait anxiety symptoms in population-based studies (see e.g.: [De Moor et al., 2006; Caravati-Jouvenceaux et al., 2011]) that has been shown to correlate highly with other anxiety measures [Spielberger and Reheiser, 2009]. The abbreviated 10-item STAI-T short form has shown excellent internal consistency reliability in the full HCHS/SOL sample ($\alpha = 0.93$) and for both the English ($\alpha = 0.92$) and Spanish ($\alpha = 0.94$) versions of the instrument [Wassertheil-Smoller et al., 2014]. It has been shown in other studies to correlate highly with the full version ($\alpha = 0.96$) [Bromberger and Matthews, 1996]. For each item, participants were asked to indicate how they generally feel (0 = almost never; 1 = sometimes; 2 = often; 3 = almost always). Using the STAI short form, we created a GAD symptoms score by summing the three items (i.e., feeling nervous or restless; worrying over things that don't matter; getting in a state of tension or turmoil as you think about recent concerns and interests) that are diagnostic criteria for GAD as defined by the DSM-5 [American Psychiatric Association, 2013]. The GAD symptoms score demonstrated moderate internal consistency reliability ($\alpha = 0.70$) in the full HCHS/SOL sample. For comparison, we also examined a total trait anxiety score based on summing responses to all 10 items (i.e., the three GAD symptom score items noted above plus the following seven items: I feel satisfied with myself; I lack self confidence; I feel secure; I feel inadequate; I am a steady person; I wish I could be as happy as others seem to be; I feel like a failure). Both phenotypes were coded so that higher scores indicated higher levels of anxiety.

To account for the possibility that current use of antidepressant or anxiolytic medications might affect anxiety scores, we applied an imputation algorithm to increase the scores of medication users. This algorithm was used in a previous GWAS of depressive symptoms [Hek et al., 2013] and was similar to an algorithm used to adjust blood pressure for persons on antihypertensive medications [Levy et al., 2000]. Antidepressant or anxiolytic medication use was determined by pill bottles brought by the participant to the baseline interview. Antidepressants were included, as this class of drugs are commonly prescribed to treat generalized anxiety symptoms [Kapczinski et al., 2003; Milea et al., 2010]. This algorithm assumed that: (i) the anxiety score of a respondent taking these psychotropic medications is lower (i.e., indicating fewer symptoms) than would be expected if the respondent were not taking these medications (thus, we assume that the medications are effective in reducing symptoms); (ii) respondents with high anxiety scores, on average, respond less to these medications than respondents with lower anxiety scores. The algorithm therefore, replaced the anxiety score of respondents on medications ($n = 1{,}068$) with the mean anxiety score of all respondents taking these medications that had the same or a higher anxiety score. For example, a medication user with an observed anxiety score of 10 would have a revised score of 21.07 (derived by taking the average anxiety score of medication users with an anxiety score value of 10 or greater). Anxiety scores for medication users were increased by 6.2 points on average above the raw score (raw scores ranged from 0 to 30).

SNP Genotyping, Quality Control, and Imputation

Blood samples from consenting respondents were sent to Illumina Microarray Services for genotyping on the Illumina SOL HCHS Custom 15041502 B3 array. This array comprised the Illumina Omni 2.5M array (HumanOmni2.5-8v1-1) and additional custom content (e.g., ancestry-informative markers, variants characteristic of Amerindian populations, known GWAS hits, and other candidate gene markers) selected for HCHS/SOL.

Quality assurance/quality control (QA/QC) was performed by Illumina, LA Biomed, and the HCHS/SOL Genetic Analysis Center (GAC) according to established methods [Laurie et al., 2010] to generate recommended SNP and sample-level quality filters. In brief, samples were checked for annotated versus genetic sex, gross chromosomal anomalies [Laurie et al., 2012], call rates, batch effects, duplicate sample discordance, Mendelian errors, population structure, and relatedness (note: participants could have been genetically related due to being drawn from the same household or different households living in the same community). Twelve thousand eight-hundred three unique study samples passed these criteria. SNPs that passed the Illumina/LA Biomed assay failure indicator were further checked for Hardy–Weinberg equilibrium, MAF, duplicate probe discordance, and missing call rate. A total of 2,232,944 SNPs passed both quality and informativeness filters (unduplicated on the array and polymorphic).

Genome-wide imputation was carried out on all 12,803 samples together using the 1000 Genomes Project phase 1 reference panel [1000 Genomes Project et al., 2012] and IMPUTE2 software [Howie et al., 2009, 2011]. Genotypes were first pre-phased with SHAPEIT2 (v2.r644) and then imputed with IMPUTE2 (v2.3.0). Only variants with at least two copies of the minor allele present in any of the four 1000 Genomes continental panels were imputed, yielding a total of 25,568,744 imputed variants. Overall imputation quality was assessed both by looking at the distribution of imputed quality metrics by different MAF levels and by examining results from the IMPUTE2 internal masking experiments (as some genotyped variants were "masked," meaning removed from the imputation basis).

Principal components (PCs) and kinship coefficients were computed in an iterative manner to estimate both population structure and relatedness between study individuals such that the PCs were not affected by relatedness, and kinship estimates are not affected by ancestry. The process began with estimating relatedness using KING-robust [Manichaikul et al., 2010], followed by iterative estimation of PCs and kinship coefficients using PC-AiR [Conomos et al., 2015] and PC-Relate (https://www.bioconductor.org/packages/release/bioc/html/GENESIS.html), and is described comprehensively elsewhere [Conomos, 2014]. Consequently, 19 individuals who were identified to have primarily east Asian ancestry were excluded from analysis. For association analysis, the kinship

matrix was based on an independent set of SNPs selected with LD pruning.

Statistical Analyses

All analyses used a linear mixed-effect model, which accounted for the correlations between individuals due to genetic relatedness (kinship), shared household, and the complex sampling design [Conomos et al., 2016; Schick et al., 2016]. The variance components were estimated using restricted maximum likelihood (REML). Fixed effects included the covariates: log (sampling weight), which reflect the differences in sampling probabilities of study individuals and is included to prevent potential selection bias; field center; age; sex; education (1 = no high school diploma or GED—referent; 2 = at most a High school diploma or GED, 3 = greater than high school or GED; 4 = bachelors degree, 5 = masters, professional, or doctorate degree); and the top five PCs of ancestry. SNP annotation was performed using ANNOVAR [Wang et al., 2010] (http://annovar.openbioinformatics.org/en/latest/).

Heritability Analysis

We estimated "SNP-chip heritability," or the narrow-sense heritability due to the additive effect of common variants (genotyped and imputed), by first fitting a "null" linear mixed model that included all covariates, PCs, and random effects, but did not include genotypes, and then calculating the proportion of variance attributable to relatedness out of all phenotypic variance [Conomos et al., 2016; Schick et al., 2016]. For this analysis, the kinship matrix was calculated based on PC-relate using all autosomal SNPs, and the model was fit on a set of 10,414 unrelated individuals by removing participants so that the unrelated set did not have first-, second-, or third-degree relatives [Yang et al., 2010]. We conducted this analysis examining the GAD symptoms score as well as the total trait anxiety score to evaluate and compare SNP-chip heritability estimates across these phenotypes.

GWAS Analysis

We performed a GWAS using the linear mixed-effect model approach. All SNPs were modeled additively and the standard 5×10^{-8} was used as the threshold for genome-wide statistical significance. In addition, we report the set of SNPs with *P*-value $< 1 \times 10^{-6}$ according to the following selection criteria: out of SNPs that were less than 500,000 base pairs apart, and their correlation was higher than 0.5, we prioritized genotyped over imputed SNPs, we preferred imputed SNPs with higher quality score (info), lower *P*-values, and for SNPs with similar *P*-values and imputation quality score (or genotyped), we prioritized SNPs with higher MAF. Quantile-quantile (QQ) and Manhattan plots were generated using the R package GWASTools [Gogarten et al., 2012]. Regional association plots were generated using Locus Zoom [Pruim et al., 2010].

Secondary Analysis

As a secondary analysis, we repeated our analyses in the subset of non-medication users (n = 11,456; 91.5% of the sample) and using an untransformed score that did not consider medication use (i.e., the raw phenotype score).

Replication

We attempted replication of these results using data from three independent cohorts. Additional details about these cohorts are presented in Supplemental Materials. Briefly, the Women's Health Initiative (The Women's Health Initiative Study Group, 1998, WHI; www.whi.org [Wassertheil-Smoller et al., 2004]) provided data on Hispanic/Latina women (n = 3,352; mean age 60.0; SD = 6.57), where anxiety symptoms were measured using a single item (i.e., have you been a very nervous person in the past four weeks). The Multi-Ethnic Study of Atherosclerosis (MESA; http://www.mesa-nhlbi.org) [Bild et al., 2002] provided data from Hispanic/Latino adults (n = 1,449; mean age 61.38; SD = 10.30) where anxiety symptoms were measured using a scale identical to the HCHS/SOL. Finally, the Army Study To Assess Risk and Resilience in Service members (Army STARRS; http://www.armystarrs.org) [Ursano et al., 2014] provided data from Hispanic/Latino adults (n = 3,394; mean age = 25.98; SD = 5.00), where anxiety symptoms were captured using a five-item scale designed to match DSM-IV criteria for GAD.

We meta-analyzed GWAS results across the three independent samples. As we were interested in testing whether the direction of effect was the same in the replication (as the discovery), one sided *P*-values were used [Heller et al., 2015]. Inverse variance weighted fixed-effect meta-analysis was conducted using METAL (http://www.sph.umich.edu/csg/abecasis/metal/;[Willer et al., 2010]).

TABLE I. Results of Genome-Wide Complex Trait Analysis

	Original scores		Accounting for medication use		Medication users removed	
	V(G)/Vp × 100	*P*-values	V(G)/Vp × 100	*P*-values	V(G)/Vp × 100	*P*-values
GAD symptoms score	7.57	0.12	7.20	0.03	8.15	0.06
Total trait anxiety score	5.65	0.32	4.97	0.20	8.18	0.14

V(G)/Vp × 100 = SNP heritability estimate (h^2_{SNP}) × 100. All phenotypes were treated as continuous. All models adjusted for sex, age, education (five-levels), principal components, study center, and sampling weights, and included random effects for the design variables kinship, household, and block unit, the three study design variables. *P*-values were calculated using the likelihood ratio test. The total trait anxiety score was derived by summing responses to all 10 items (see Supplemental Materials for listing of all items). The GAD symptoms score was based on summing three items (i.e., feeling nervous or restless; worrying over things that don't matter; getting in a state of tension or turmoil as you think about recent concerns and interests) that are diagnostic criteria for GAD as defined by the DSM-V.

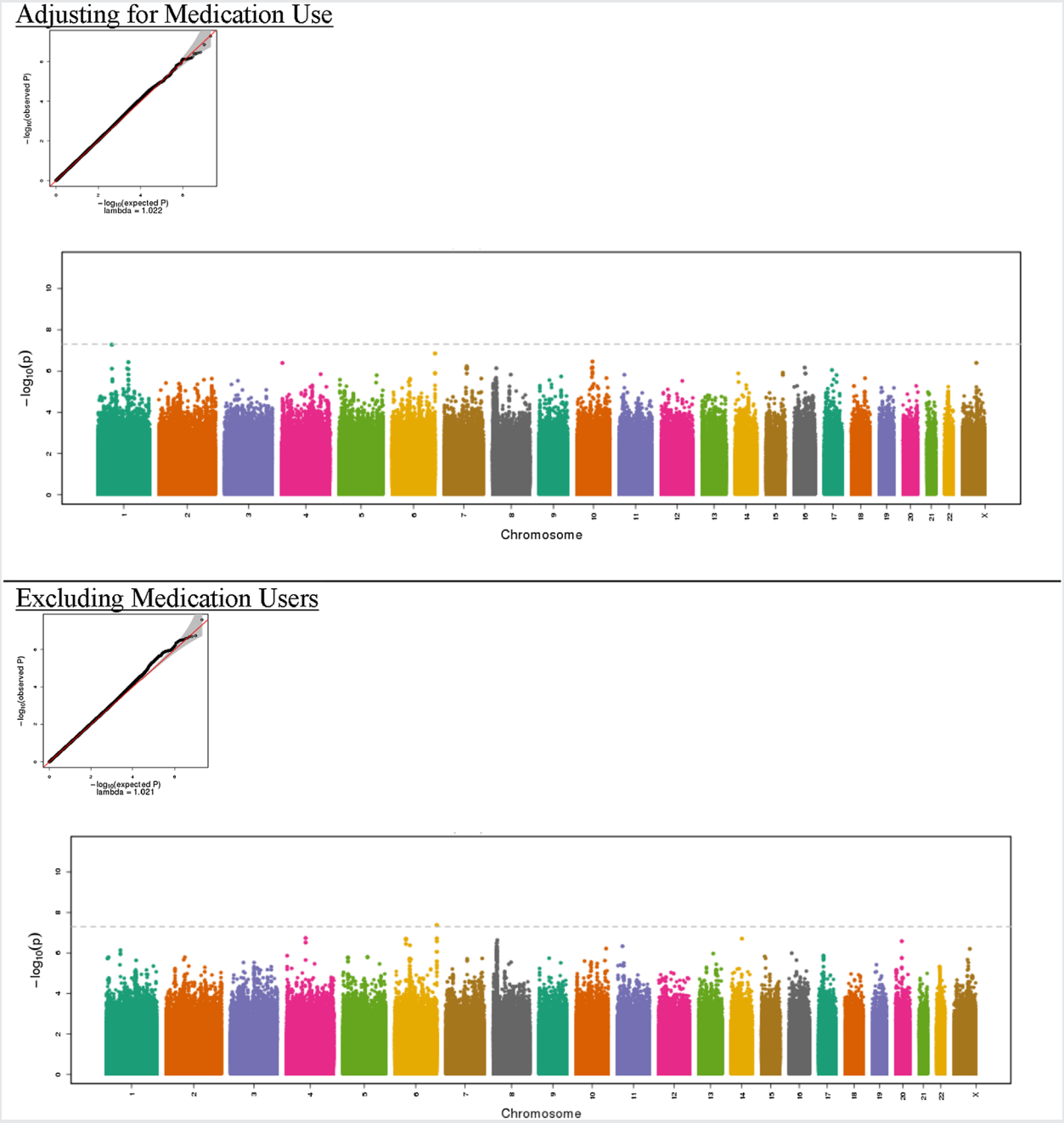


FIG. 1. Quantile–quantile (QQ) plots and Manhattan plots for GAD symptoms score from the Hispanic Community Health Study/Study of Latinos. The quantile–quantile plots ("QQ-plots"), which present the observed by expected *P*-values on the −log10 scale, indicate conformity of the observed results to what would be expected under the null. In the Manhattan plots, the *x*-axis is the chromosomal position and the *y*-axis is the −log10 *P*-value for the association between each SNP and the GAD symptoms score derived from the linear regression model. The dotted line shows the genome-wide significance level ($5 \times 10-8$). The displayed *P*-value corresponds to SNPs with effective N > 30.

RESULTS

A total of 12,282 Hispanic/Latino respondents were in the analysis. As expected, the GAD symptom score (skew = 0.63; kurtosis = 2.48) and total trait anxiety score (skew = 0.87; kurtosis = 3.21) were skewed towards lower values. No transformations of the outcome were performed as linear regression is robust to minor violations of normality [van Belle, 2002].

TABLE II. Genome-Wide Association Study (GWAS) Results for the Top Loci ($P < 1 \times 10^{-6}$) with the GAD Symptoms Score Imputed for Medication Use

SNP	CHR	Position	AlleleA	AlleleB	MAF	Minor allele	Geno.	n	Beta	SE	*P*-value	Location	Closest gene (<20 kb)
rs10749727	1	62056653	A	G	0.002	A	I	12,282	1.97	0.36	5.28E-08		
rs78602344	6	169626581	T	C	0.113	B	G	12,282	−0.26	0.05	1.41E-07	Intronic	*THBS2*
rs10994985	10	63713219	T	C	0.046	B	G	12,282	−0.38	0.08	3.48E-07		
rs3753389	1	160807153	T	C	0.378	A	I	12,282	−0.16	0.03	3.70E-07	Intronic	*CD244*
rs12353562	X	96354053	G	A	0.099	B	I	12,269	−0.23	0.05	4.04E-07	Intronic	*DIAPH2*
rs144417828	4	3740444	G	A	0.010	B	I	12,282	−0.84	0.17	4.07E-07		
rs148349076	16	54271147	C	T	0.004	B	I	12,282	−1.29	0.26	6.78E-07		
rs7094998	10	61306319	A	G	0.210	B	G	12,282	0.19	0.04	7.13E-07		
rs17729883	8	9256631	T	C	0.220	B	G	12,281	−0.19	0.04	7.29E-07		
rs11803917	1	156111578	C	T	0.071	B	I	12,282	0.32	0.06	7.41E-07		
rs75192612	7	88641306	A	G	0.004	B	I	12,282	−1.19	0.24	7.49E-07		
rs3110650	17	36075905	T	C	0.002	A	I	12,282	1.86	0.38	8.94E-07		

CHR, chromosome. In the geno. (genotyping) column, G, genotyped and I, imputed. All imputed SNPs had info scores (indicating imputation quality) ≥ 0.70. AlleleA is the tested allele. Position is given in genome build GRCh37/hg19.

TABLE III. Genome-Wide Association Study (GWAS) Results for the Top Loci ($P < 1 \times 10^{-6}$) with the GAD Symptoms Score, After Excluding Medication Users

SNP	CHR	Position	AlleleA	AlleleB	MAF	Minor allele	Geno.	n	Beta	SE	*P*-value	Location	Closest gene (<20 kb)
rs78602344	6	169626581	T	C	0.115	B	G	11,456	−0.27	0.05	4.18E-08	Intronic	*THBS2*
rs141474992	4	75958947	A	C	0.006	B	I	11,456	−1.04	0.20	1.83E-07		
rs79812562	14	64593580	C	A	0.008	B	I	11,456	−1.02	0.20	1.95E-07		
rs146964092	6	39754875	A	G	0.001	B	I	11,456	−2.16	0.42	1.96E-07		
rs7350124	8	10625045	T	C	0.182	B	I	11,455	−0.21	0.04	2.34E-07	Intronic	*PINX1*
rs186222942	20	24548719	G	A	0.012	B	I	11,456	−0.77	0.15	2.61E-07		
rs11776020	8	8809696	A	G	0.455	B	G	11,455	−0.17	0.03	3.26E-07		
rs115013535	6	55628681	C	A	0.004	B	I	11,456	−1.30	0.26	4.16E-07		
rs186294317	11	20267060	G	A	0.002	B	I	11,456	−1.86	0.37	4.62E-07		
rs17729883	8	9256631	T	C	0.216	B	G	11,455	−0.19	0.04	5.09E-07		
rs189738814	10	126827710	G	A	0.004	B	I	11,456	−1.50	0.30	6.02E-07		
rs144369074	X	113716176	A	T	0.005	B	I	11,445	−1.03	0.21	6.24E-07		
rs115791358	1	64300191	A	T	0.004	B	I	11,456	−1.23	0.25	7.24E-07		
rs11756502	6	169633185	C	T	0.315	B	G	11,456	−0.16	0.03	8.66E-07	Intronic	*THBS2*
rs62435218	6	169642301	C	T	0.179	B	G	11,456	−0.20	0.04	8.74E-07	Intronic	*THBS2*
rs6601288	8	8943430	A	T	0.484	A	G	11,455	−0.16	0.03	9.59E-07		

CHR, chromosome. In the geno. (genotyping) column, G, genotyped and I, imputed. All imputed SNPs had info scores (indicating imputation quality) ≥ 0.62. AlleleA is the tested allele. Position is given in genome build GRCh37/hg19.

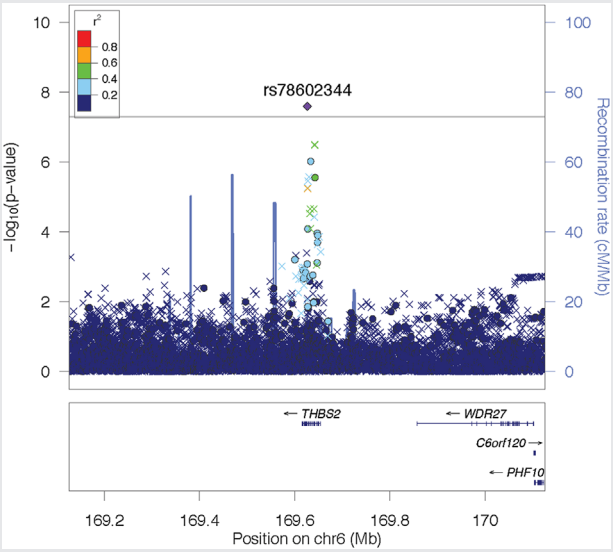


FIG. 2. Regional association plot for the top SNP (rs78602344) identified in the analysis excluding medication users. The regional association plot was generated using LocusZoom (http://csg.sph.umich.edu/locuszoom/) The left-side *y*-axis refers to the -log of the *P*-value corresponding to the test of association between each SNP (denoted as a colored dot, if genotyped, or X, if imputed) and GAD symptoms. SNPs are colored based on the level of linkage disequilibrium (LD) between each SNP and the index, genotyped, SNP (purple diamond). r2 values are determined based on the HCHS/SOL data.

Discovery Sample: SNP Heritability

As shown in Table I, the GAD symptom score showed evidence of modest heritability ($h^2_{SNP} = 7.2\%$; $P = 0.03$), while the total trait anxiety score did not ($h^2_{SNP} = 4.97\%$; $P = 0.20$). Building from these results, we conducted a GWAS only on the GAD symptom score.

Discovery Sample: GWAS

The Manhattan and QQ plots are shown in Figure 1. As shown in the QQ plots, there was no evidence of inflation in either the GWAS of the full sample or the analysis that excluded medication users ($\lambda = 1.02$). No SNPs achieved genome-wide significance in the full sample, which included imputed scores for medication users (Table II). However, one genotyped SNP (rs78602344), located on chromosome six at position 169626581, emerged from both analyses. This SNP was the second most significant result in the full sample ($P = 1.41 \times 10^{-7}$) and the most significant result ($P = 4.18 \times 10^{-8}$) in the analysis excluding medication users (Table III). The SNP is intronic to thrombospondin 2 (*THBS2*), a gene that mediates cell-to-cell and cell-to-matrix interactions. Several other SNPs in the region also showed support for association (Fig. 2).

A second SNP with a low *P*-value in both analyses was rs17729883 (full sample $P = 7.29 \times 10^{-7}$; excluding medication users $P = 5.09 \times 10^{-7}$) located on chromosome eight. This genotyped SNP was located in an intron of an uncharacterized gene (LOC 106379231; Supplemental Fig. S1).

All GWAS results at $P < 1 \times 10^{-5}$ are shown in the Supplemental Materials for the GAD symptom score for the full sample (Supplemental Table SI), excluding medication users (Supplemental Table SII), and for the original, non-transformed score (Supplemental Table SIII).

To determine which SNPs to carry forward for replication, we estimated replication power for all SNPs with *P*-values $<1 \times 10^{-6}$ in at least one of the two analyses according to our selection criteria detailed above. Replication power estimates were based on the projected samples sizes of each replication dataset (WHI = 3,000; MESA = 1,500; Army STARRS = 3,000) and using MAF, outcome standard deviation, and estimated effect sizes from the discovery sample. Our power calculations incorporated a method [Zhong and Prentice, 2008] to reduce bias due to "winner's curse," effectively attenuating the observed effect size. A prior study showed that attenuated effect size estimates tend to be closer than uncorrected estimates to effects seen in independent replication studies [Zhong and Prentice, 2010].

Our power analysis suggested that one SNP [rs78602344) would have excellent power in a meta analysis of the three replication cohorts after the winner's curse bias correction (estimated power = 0.96); all other SNPs had weak power ($\leq$0.70). We therefore carried forward this single SNP for replication.

Replication Samples: GWAS Results

In the replication phase, one SNP [rs78602344) was evaluated in three independent samples. This SNP was not significantly associated with the GAD symptom score in a meta analysis of the replication sites (Table IV).

DISCUSSION

The current study involved three major innovations in efforts to identify the genetic basis of generalized anxiety. First, to our knowledge, this was the first GWAS of GAD symptoms. Prior genetic association studies of GAD have focused on candidate gene polymorphisms, most of which have showed inconsistent results [Smoller, 2016]. Among GWAS, extant studies have focused on other anxiety disorders, including post-traumatic stress disorder [Guffanti et al., 2013; Logue et al., 2013; Xie et al., 2013] and panic disorder [Otowa et al., 2009, 2010; Erhardt et al., 2011], or have examined more global symptoms of trait anxiety in children [Trzaskowski et al., 2013] or composite indicators of anxiety disorder in adults [Otowa et al., 2014], but have not yet examined general symptoms of anxiety in adults. Second, our study was also the first to provide SNP-chip heritability estimates of GAD symptoms. Such analyses are important to provide upper- and lower-bound estimates of the additive genetic contribution to GAD. Finally, we conducted these genetic association analyses in Hispanics/Latinos, a large and growing US population group. Previous studies have largely focused on individuals of European ancestry.

TABLE IV. Replication Results of rs78602344 for GAD Symptoms

A. Adjusting for medication use

	SNP	CHR	Position	AlleleA	AlleleB	MAF	Minor allele	Geno.	n	Beta	SE	*P*-value
Discovery	**rs78602344**	**6**	**169626581**	**T**	**C**	**0.113**	**C**	**G**	**12,282**	**−0.26**	**0.05**	**1.41E-07**
Army NSS1	rs78602344	6	169626581	T	C	0.108	C	I	1,408	0.11	0.34	0.76
Army NSS2	rs78602344	6	169626581	T	C	0.111	C	I	453	1.38	0.68	0.04
Army PPDS	rs78602344	6	169626581	T	C	0.108	C	I	1,533	0.17	0.30	0.57
MESA	rs78602344	6	169626581	T	C	0.133	C	I	1,441	0.02	0.06	0.73
WHI	rs9505953	6	108969803	C	T	0.206	T	I	2,950	—	0.04	0.54
Meta analysis				T	C				7,785	0.03	0.03	0.43

B. Excluding medication users

	SNP	CHR	Position	AlleleA	AlleleB	MAF	Minor allele	Geno.	n	Beta	SE	*P*-value
Discovery	**rs78602344**	**6**	**169626581**	**T**	**C**	**0.113**	**C**	**G**	**11,456**	**−0.27**	**0.05**	**4.18E-08**
Army NSS1	rs78602344	6	169626581	T	C	0.108	C	I	1,372	0.11	0.34	0.74
Army NSS2	rs78602344	6	169626581	T	C	0.111	C	I	431	1.00	0.66	0.13
Army PPDS	rs78602344	6	169626581	T	C	0.108	C	I	1,430	−0.04	0.27	0.88
MESA	rs78602344	6	169626581	T	C	0.133	C	I	1,369	0.01	0.07	0.92
WHI	rs9505953	6	108969803	C	T	0.205	T	I	2,513	−0.01	0.04	0.77
Meta analysis				T	C				7,115	0.01	0.03	0.71

CHR, chromosome. In the geno. (genotyping) column, G, genotyped and I, imputed. All imputed SNPs had info scores (indicating imputation quality) >0.83. AlleleA is the tested allele. The Army STARRs dataset comprised three different cohorts: the New Soldiers Study 1, the New Soldiers Study 2, and the Post-Deployment Study. The SNP identified in the discovery analysis and carried forward to the replication (rs78602344) was neither genotyped nor imputed in WHI. We, therefore, used the best proxy SNP (rs9505953) in closest LD ($r^2 = 0.15$).

Two findings emerged from the current study. First, results from the SNP-chip heritability analysis suggested that about 7.2% of the variance in GAD symptoms was explained by common genetic variants. This SNP heritability estimate is lower than those found for phobic anxiety ($h^2_{SNP} = 21\%$; $P = 0.01$) [Walter et al., 2013] and anxiety sensitivity ($h^2_{SNP} = 45\%$; 95%CI = 32%, 56%) [Davies et al., 2015] in adults, and also lower relative to estimates for a composite measure of anxiety traits in children, which was derived by summing measures of negative affect, negative cognition, fear, and social anxiety ($h^2_{SNP} = 16\%$; $P = 0.07$) [Trzaskowski et al., 2013]. The lower heritability estimates observed in this study relative to other studies conducted in adults may be due to the use of symptom scale, rather than a diagnostic measure of GAD. Interestingly, we also found that the total trait anxiety score, derived by summing all items on the scale (rather than just the three corresponding to GAD symptoms) carried no significant heritable signal. This result suggests that not all symptoms on existing anxiety scales may be equally influenced by additive genetic variation. Future studies using dimensional measures of anxiety symptoms may benefit from conducting similar analyses to determine whether an existing scale should be used in its entirety.

Second, we identified one genotyped SNP (rs78602344) located on chromosome six that was common to analyses accounting for psychiatric medication use or excluding medication users. Although not genome-wide significant in the former analysis, this SNP was genome-wide significant after excluding medication users ($P = 4.18 \times 10^{-8}$). This SNP is intronic to thrombospondin 2 (*THBS2*), a gene that mediates cell-to-cell and cell-to-matrix interactions. Several other SNPs in the region also showed support for association. However, this association was not supported in a meta-analysis of the three independent Hispanic/Latino replication samples ($n > 7{,}000$). We suspect that GWAS of GAD symptoms will likely share a similar trajectory as depressive symptoms, where increasing larger sample sizes and refinement of the phenotype will lead to the identification of associated loci [CONVERGE Consortium, 2015; Dunn et al., 2015].

We note several limitations of the current study. First, the outcomes were based on a brief inventory of trait anxiety symptoms. Although the widespread use of this anxiety measure in population-based studies allowed us to carry out the current analyses, future studies of diagnostic measures of GAD as well as more robust measures of GAD symptoms (from more detailed and specific measures or repeated phenotyping) are needed. Second, the replication samples were smaller and both more demographically and phenotypically heterogeneous than the HCHS/SOL discovery sample. Unfortunately, replication efforts are currently hampered by a lack of available data on anxiety symptoms in racial/ethnic minority populations. Third and relatedly, only one SNP was carried forward to the replication phase. This single SNP was the only one with high replication power. Moreover, greater insights are needed regarding the most optimal strategy to account for medication use in genetic association studies of quantitative traits. Future studies are needed to examine the suitability of different techniques and the extent to which different adjustment methods lead to different results (e.g., whether they substantially reduce variance if a substantial portion of the sample is assigned the same score; whether empirical data, such as medication efficacy, can be used to inform the adjustment strategy).

In conclusion, although the GWAS revealed a genome-wide significant locus in the discovery sample, we were unable to replicate this in independent samples. These findings underscore the need for even larger studies of GAD symptoms.

ACKNOWLEDGMENTS

The Hispanic Community Health Study/Study of Latinos (HCHS/SOL) was carried out as a collaborative study supported by contracts from the National Heart, Lung, and Blood Institute (NHLBI) to the University of North Carolina (N01- HC65233), University of Miami (N01-HC65234), Albert Einstein College of Medicine (N01-HC65235), Northwestern University (N01-HC65236), and San Diego State University (N01-HC65237). The following Institutes/Centers/Offices contribute to the HCHS/SOL through a transfer of funds to the NHLBI: National Institute on Minority Health and Health Disparities, National Institute on Deafness and Other Communication Disorders, National Institute of Dental and Craniofacial Research, National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Neurological Disorders and Stroke, NIH Institution-Office of Dietary Supplements. MESA and the MESA SHARe project are conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with MESA investigators. Support for MESA is provided by contracts N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168, N01-HC-95169, UL1-TR-001079, UL1-TR-000040, and DK063491. The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts HHSN268201100046C, HHSN268201100001C, HHSN26 8201100002C, HHSN268201100003C, HHSN268201100004C, and HHSN271201100004C. The Army Study of Risk and Resilience in Servicemembers (Army STARRS) was sponsored by the Department of the Army and funded under cooperative agreement number U01MH087981 with the U.S. Department of Health and Human Services, National Institutes of Health, and National Institute of Mental Health (NIH/NIMH).

The contents are solely the responsibility of the authors and do not necessarily represent the views of the Department of Health and Human Services, the National Institutes of Health, the Veterans Administration, Department of the Army, or the Department of Defense.

The current study is supported the National Institute of Mental Health of the National Institutes of Health under Award Number K01MH102403 (Dunn) and K24MH094614 (Smoller), by a NARSAD Young Investigator Grant from the Brain & Behavior Research Foundation (Dunn), and a Tepper Family MGH Research Scholar Award (Smoller).

The authors thank Sandy Li and Jenna Kiely for their assistance in conducting the literature search for this paper. The authors also thank the staff and participants of HCHS/SOL for their important contributions. A complete list of staff and investigators has been provided by Lavange et al. [2010] and is also available on the study website http://www.cscc.unc.edu/hchs/.

REFERENCES

American Psychiatric Association. 2013. Diagnostic and statistical manual of mental disorders. Arlington, VA: American Psychiatric Publishing.

Asnaani A, Richey JA, Dimaite R, Hinton DE, Hofmann SG. 2010. A cross-ethnic comparison of lifetime prevalence rates of anxiety disorders. J Nerv Mental Dis 198(8):551–555.

Bergua V, Meillon C, Potvin O, Ritchie K, Tzourio C, Bouisson J, Dartigues JF, Amieva H. 2015. Short STAI-Y anxiety scales: Validation and normative data for elderly subjects. Aging Ment Health 1–9. [Epub ahead of print].

Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, Greenland P, Jacob DR Jr., Kronmal R, Liu K, Nelson JC, O'Leary D, Saad MF, Shea S, Szklo M, Tracy RP. 2002. Multi-ethnic study of atherosclerosis: Objectives and design. Am J Epidemiol 156(9):871–881.

Bromberger JT, Matthews KA. 1996. A longitudinal study of the effects of pessimism, trait anxiety, and life stress on depressive symptoms in middle-aged women. Psychol Aging 11(2):207–213.

Brown A. 2014. U.S. Hispanic and Asian populations growing, but for different reasons. http://www.pewresearch.org/fact-tank/2014/06/26/u-s-hispanic-and-asian-populations-growing-but-for-different-reasons/

Caravati-Jouvenceaux A, Launoy G, Klein D, Henry-Amar M, Abeilard E, Danzon A, Pozet A, Velten M, Mercier M. 2011. Health-related quality of life among long-term survivors of colorectal cancer: A population-based study. Oncologist 16:1626–1636.

Conomos MP. 2014. Inferring, estimating and accounting for population and pedigree structure in genetic analyses. PhD, University of Washington.

Conomos MP, Laurie CA, Stilp AM, Gogarten SM, McHugh CP, Nelson SC, Sofer T, Fernandez-Rhodes L, Justice AE, Graff M, Young KL, Seyerle AA, Avery CL, Taylor KD, Rotter JI, Talavera GA, Daviglus ML, Wassertheil-Smoller S, Schneiderman N, Heiss G, Kaplan RC, Franceschini N, Reiner AP, Shaffer JR, Barr RG, Kerr KF, Browning SR, Browning BL, Weir BS, Aviles-Santa ML, Papanicolaou GJ, Lumley T, Szpiro AA, North KE, Rice K, Thornton TA, Laurie CC. 2016. Genetic diversity and association studies in US Hispanic/Latino populations: Applications in the Hispanic Community Health Study/Study of Latinos. Am J Hum Genet 98(1):165–184.

Conomos MP, Miller MB, Thorton TA. 2015. Robust inference of population structure for ancestry prediction and correction of stratification in the presence of relatedness. Genet Epidemiol 39(4):276–293.

CONVERGE Consortium. 2015. Sparse whole-genome sequencing identifies two loci for major depressive disorder. Nature 523(7562):588–591.

Davies MN, Verdi S, Burri A, Trzaskowski M, Lee M, Hettema J M, Jansen R, Boomsma DI, Spector TD. 2015. Generalised anxiety disorder–A twin study of genetic architecture, genome-wide association and differential gene expression. PLoS ONE 10(8):e0134865.

De Moor MH, Beem AL, Stubbe JH, Boomsma DI, De Geus EJ. 2006. Regular exercise, anxiety, depression and personality: A population-based study. Prev Med 42(4):273–279.

Dunn EC, Brown RC, Dai Y, Rosand J, Nugent NR, Amstadter AB, Smoller JW. 2015. Genetic determinants of depression: Recent findings and future directions. Harv Rev Psychiatry 23(1):1–18.

Erhardt A, Czibere L, Roeske D, Lucae S, Unschuld PG, Ripke S, Specht M, Kohli MA, Kloiber S, Ising M, et al. 2011. TMEM132D, a new candidate for anxiety phenotypes: Evidence from human and mouse studies. Mol Psychiatry 16(6):647–663.

1000 Genomes Project Consortium, Abecasis GR, Auton A, Brooks LD, DePristo MA, Durbin RM, Handsaker RE, Kang HM, Marth GT, McVean GA. 2012. An integrated map of genetic variation from 1,092 human genomes. Nature 491(7422):56–65.

Gogarten SM, Bhangale T, Conomos MP, Laurie CA, McHugh CP, Painter I, Zheng X, Crosslin DR, Levine D, Lumley T, Nelson SC, Rice K, Shen J, Swarnkar R, Weir BS, Laurie CC. 2012. GWASTools: An R/Bioconductor package for quality control and analysis of genome-wide association studies. Bioinformatics 28(24):3329–3331.

Grant BF, Hasin DS, Stinson FS, Dawson DA, Ruan WJ, Goldstein RB, Smith SM, Saha TD, Huang B. 2005. Prevalence, correlates, co-morbidity, and comparative disability of DSM-IV generalized anxiety disorder in the USA: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. Psychol Med 35:1747–1759.

Guffanti G, Galea S, Yan L, Roberts AL, Solovieff N, Aiello AE, Smoller JW, De Vivo I, Ranu H, Uddin M, et al. 2013. Genome-wide association study implicates a novel RNA gene, the lincRNA AC068718.1, as a risk factor for post-traumatic stress disorder in women. Psychoneuroendocrinology 38(12):3029–3038.

Hek K, Demirkan A, Lahti J, Terracciano A, Teumer A, Cornelis MC, Amin N, Bakshis E, Baumert J, Ding J, Liu Y, Marciante K, Meirelles O, Nalls MA, Sun YV, Vogelzangs N, Yu L, Bandinelli S, Benjamin EJ, Bennett DA, Boomsma D, Cannas A, Coker LH, de Geus E, De Jager PL, Diez-Roux AV, Purcell S, Hu FB, Rimm EB, Hunter DJ, Jensen MK, Curhan G, Rice K, Penman AD, Rotter JI, Sotoodehnia N, Emeny R, Eriksson JG, Evans DA, Ferrucci L, Fornage M, Gudnason V, Hofman A, Illig T, Kardia S, Kelly-Hayes M, Koenen K, Kraft P, Kuningas M, Massaro JM, Melzer D, Mulas A, Mulder CL, Murray A, Oostra BA, Palotie A, Penninx B, Petersmann A, Pilling LC, Psaty B, Rawal R, Reiman EM, Schulz A, Shulman JM, Singleton AB, Smith AV, Sutin AR, Uitterlinden AG, Volzke H, Widen E, Yaffe K, Zonderman AB, Cucca F, Harris T, Ladwig KH, Llewellyn DJ, Raikkonen K, Tanaka T, van Duijn CM, Grabe HJ, Launer LJ, Lunetta KL, Mosley TH Jr., Newman AB, Tiemeier H, Murabito J. 2013. A genome-wide association study of depressive symptoms. Biol Psychiatry 73(7):667–678.

Heller R, Bogomolov M, Benjamini Y, Sofer T. 2015. Testing for replicability in a follow-up study when the primary study hypotheses are two-sided. http://arxiv.org/abs/1503.02278.

Hettema JM, Neale MC, Kendler KS. 2001. A review and meta-analysis of the genetic epidemiology of anxiety disorders. Am J Psychiatry 158:1568–1578.

Hoffman DL, Dukes EM, Wittchen HU. 2008. Human and economic burden of generalized anxiety disorder. Depress Anxiety 25(1):72–90.

Hoge EA, Ivkovic A, Frichione GL. 2012. Generalized anxiety disorder: Diagnosis and treatment. Br Med J 345:37500.

Howie BN, Donnelly P, Marchini J. 2009. A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. PLoS Genet 5(6):e1000529.

Howie BN, Marchini J, Stephens M. 2011. Genotype imputation with thousands of genomes. G3 (Bethesda) 1:457–470.

Kapczinski FFK, Silva de Lima M, dos Santos Souza JJSS, Batista Miralha da Cunha AABC, Schmitt RRS. 2003. Antidepressants for generalized anxiety disorder. Cochrane Database Syst Rev 2:CD003592.

Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. 2005a. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 62(6):593–602.

Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. 2005b. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 62(6):617–627.

Laurie CC, Doheny KF, Mirel DB, Pugh EW, Bierut LJ, Bhangale T, Boehm F, Caporaso NE, Cornelis MC, Edenberg HJ, Gabriel SB, Harris EL, Hu FB, Jacobs KB, Kraft P, Landi MT, Lumley T, Manolio TA, McHugh C, Painter I, Paschall J, Rice JP, Rice KM, Zheng X, Weir BS, Investigators G.

2010. Quality control and quality assurance in genotypic data for genome-wide association studies. Genet Epidemiol 34(6):591–602.

Laurie CC, Laurie CA, Rice K, Doheny KF, Zelnick LR, McHugh CP, Ling H, Hetrick KN, Pugh EW, Amos C, Wei Q, Wang LE, Lee JE, Barnes KC, Hansel NN, Mathias R, Daley D, Beaty TH, Scott AF, Ruczinski I, Scharpf RB, Bierut LJ, Hartz SM, Landi MT, Freedman ND, Goldin LR, Ginsburg D, Li J, Desch KC, Strom SS, Blot WJ, Signorello LB, Ingles SA, Chanock SJ, Berndt SI, Le Marchand L, Henderson BE, Monroe KR, Heit JA, de Andrade M, Armasu SM, Regnier C, Lowe WL, Hayes MG, Marazita ML, Feingold E, Murray JC, Melbye M, Feenstra B, Kang JH, Wiggs JL, Jarvik GP, McDavid AN, Seshan VE, Mirel DB, Crenshaw A, Sharopova N, Wise A, Shen J, Crosslin DR, Levine DM, Zheng X, Udren JI, Bennett S, Nelson SC, Gogarten SM, Conomos MP, Heagerty P, Manolio T, Pasquale LR, Haiman CA, Caporaso N, Weir BS. 2012. Detectable clonal mosaicism from birth to old age and its relationship to cancer. Nat Genet 44(6):642–650.

Lavange LM, Kalsbeek WD, Sorlie PD, Aviles-Santa LM, Kaplan RC, Barnhart J, Liu K, Giachello A, Lee DJ, Ryan J, Criqui MH, Elder JP. 2010. Sample design and cohort selection in the Hispanic Community Health Study/Study of Latinos. Ann Epidemiol 20(8):642–649.

Levy D, DeStefano AL, Larson MG, O'Donnell CJ, Lifton RP, Gavras H, Cupples LA, Myers RH. 2000. Evidence for a gene influencing blood pressure on chromosome 17: Genome scan linkage results for longitudinal blood pressure phenotypes in subjects from the Framingham Heart Study. Hypertension 36(4):477–483.

Logue MW, Baldwin C, Guffanti G, Melista E, Wolfe EJ, Reardon AF, Uddin M, Wildman D, Galea S, Koenen KC, Miller MW. 2013. A genome-wide association study of post-traumatic stress disorder identifies the retinoid-related orphan receptor alpha (RORA) gene as a significant risk locus. Mol Psychiatry 18(8):937–942.

Manichaikul A, Mychaleckyj JC, Rich SS, Daly K, Sale M, Chen WM. 2010. Robust relationship inference in genome-wide association studies. Bioinformatics 26(22):2867–2873.

Milea D, Verpillat P, Guelfucci F, Toumi M, Lamure M. 2010. Prescription patterns of antidepressants: Findings from a US claims database. Curr Med Res Opin 26(6):1343–1353.

Moffitt TE, Caspi A, Taylor A, Kokaua J, Milne BJ, Polanczyk G, Poulton R. 2010. How common are common mental disorders? Evidence that lifetime prevalence rates are doubled by prospective versus retrospective ascertainment. Psychol Med 40:899–909.

Newman MG, Llera SJ, Erickson TM, Przeworski A, Castonguay LG. 2013. Worry and generalized anxiety disorder: A review and theoretical synthesis of evdience on nature, etiology, mechanisms, and treatment. Annu Rev Clin Psychol 9:275–297.

Otowa T, Maher BS, Aggen SH, McClay JL, van den Oord EJ, Hettema JM. 2014. Genome-wide and gene-based association studies of anxiety disorders in European and African American samples. PLoS ONE 9(11):e112559.

Otowa T, Tanii H, Sugaya N, Yoshida E, Inoue K, Yasuda S, Shimada T, Kawamura Y, Tochigi M, Minato T, et al. 2010. Replication of a genome-wide association study of panic disorder in a Japanese population. J Hum Genet 55(2):91–96.

Otowa T, Yoshida E, Sugaya N, Yasuda S, Nishimura Y, Inoue K, Tochigi M, Umekage T, Miyagawa T, Nishida N, et al. 2009. Genome-wide association study of panic disorder in the Japanese population. J Hum Genet 54(2):122–126.

Passel JS, Cohn DV, Lopez MH. 2011. Census 2010: 50 million Latinos, Hispanics account for more than half of nation's growth in past decade, Pew Research Center. Pew Hispanic Center.

Plomin R, Haworth CM, Davis OS. 2009. Common disorders are quantitative traits. Nat Rev Genet 10:872–878.

Pruim RJ, Welch RP, Sanna S, Teslovich TM, Chines PS, Gliedt TP, Boehnke M, Abecasis GR, Willer CJ. 2010. LocusZoom: Regional visualization of genome-wide association scan results. Bioinformatics 26(18):2336–2337.

Schick UM, Jain D, Hodonsky CJ, Morrison JV, Davis JP, Brown L, Sofer T, Conomos MP, Schurmann C, McHugh CP, Nelson SC, Vadlamudi S, Stilp A, Plantinga A, Baier L, Bien SA, Gogarten SM, Laurie CA, Taylor KD, Liu Y, Auer PL, Franceschini N, Szpiro A, Rice K, Kerr KF, Rotter JI, Hanson RL, Papanicolaou G, Rich SS, Loos RJ, Browning BL, Browning SR, Weir BS, Laurie CC, Mohlke KL, North KE, Thornton TA, Reiner AP. 2016. Genome-wide association study of platelet count identifies ancestry-specific loci in Hispanic/Latino Americans. Am J Hum Genet 98(2):229–242.

Shimada-Sugimoto M, Otowa T, Hettema JM. 2015. Genetics of anxiety disorders: Genetic epidmeiological and molecular studies in humans. Psychiatry Clin Neurosci 69(7):388–401.

Smoller JW. 2016. The genetics of stress-related disorders: PTSD, depression, and anxiety disorders. Neuropsychopharmacology 41(1):297–319.

Spielberger CD. 1989. State-trait anxiety inventory: Bibliography, 2nd edition. Palo Alto, CA: Consulting Psychologists Press.

Spielberger CD, Reheiser EC. 2009. Assessment of emotions: Anxiety, anger, depression, and curiosity. Appl Psychol Health Well Being 1(3):271–302.

Stein MB, Sareen J. 2015. Clinical practice. Generalized anxiety disorder. N Engl J Med 373(21):2059–2068.

Trzaskowski M, Eley TC, Davis OS, Doherty SJ, Hanscombe KB, Meaburn EL, Haworth CM, Price T, Plomin R. 2013. First genome-wide association study on anxiety-related behaviours in childhood. PLoS ONE 8(4): e58676.

Ursano RJ, Colpe LJ, Heeringa SG, Kessler RC, Schoenbaum M, Stein MB, Army STARRS Collaborators. 2014. The Army study to assess risk and resilience in servicemembers (Army STARRS). Psychiatry 77(2):107–119.

van Belle G. 2002. STRUTS: Statistical rules of thumb. New York, NY; John Wiley and Sons.

Walter S, Glymour MM, Koenen K, Liang L, Tchetgen Tchetgen EJ, Cornelis M, Chang SC, Rimm E, Kawachi I, Kubzansky LD. 2013. Performance of polygenic scores for predicting phobic anxiety. PLoS ONE 8(11):e80326.

Wang K, Li M, Hakonarson H. 2010. ANNOVAR: Functional annotation of genetic variants from next-generation sequencing data. Nucleic Acids Res 38(3):e164.

Wassertheil-Smoller S, Arredondo E, Cai J, Castenada S, Choca JP, Gallo L, Jung M, LaVange LM, Lee-Rey ET, Mosley T Jr., Penedo FJ, Santistaban D, Zee P. 2014. Depression, anxiety, antidepressant use, and cardiovascular disease among Hispanic men and women of different ethnic backgrounds: Results from the Hispanic Community Health Study/ Study of Latinos (HCHS/SOL). Ann Epidemiol 11:822–830.

Wassertheil-Smoller S, Shumaker S, Ockene J, Talavera GA, Greenland P, Cochrane B, Robbins J, Aragaki A, Dunbar-Jacob J. 2004. Depression and cardiovascular sequela in postmenopausal women: The Women's Health Initiative (WHI). Arch Intern Med 164:289–298.

Willer CJ, Li Y, Abecasis GR. 2010. METAL: Fast and efficient meta-analysis of genomewide association scans. Bioinformatics 26(17):2190–2191.

Wittchen HU, Jacobi F. 2005. Size and burden of mental disorders in Europe: A critical review and approaisal of 27 studies. Eur Neuropsychopharmacol 357–376.

Wittchen HU, Jacobi F, Rehm J, Gustavsson A, Svensson M, Jonsson B, Olesen J, Allgulander C, Alonso J, Faravelli C, Fratiglioni L, Jennum P, Lieb R, Maercker A, van Os J, Preisig M, Salvador-Carulla L, Simon R, Steinhausen HC. 2011. The size and burden of mental disorders and

other disorders of the brain in Europe 2010. Eur Neuropsychopharmacol 21(9):655–679.

The Women's Health Initiative Study Group. 1998. Design of the women's health initiative clinical trial and observational study. The Women's Health Initiative Study Group. Control Clin Trials 19:61–109.

Xie P, Kranzler HR, Yang C, Zhao H, Farrer LA, Gelernter J. 2013. Genome-wide association study identifies new susceptibility loci for posttraumatic stress disorder. Biol Psychiatry 74(9):656–663.

Yang J, Benyamin B, McEvoy BP, Gordon S, Henders AK, Nyholt DR, Madden PA, Heath AC, Martin NG, Montgomery GW, Goddard ME, Visscher PM. 2010. Common SNPs explain a large proportion of the heritability for human height. Nat Genet 42(7):565–569.

Zhong H, Prentice RL. 2008. Bias-reduced estimators and confidence intervals for odds ratios in genome-wide association studies. Biostatistics 9(4):621–634.

Zhong H, Prentice RL. 2010. Correcting "winner's curse" in odds ratios from genomewide association findings for major complex human diseases. Genet Epidemiol 34(1):78–91.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web-site.

Supplemental Materials
Genome-Wide Association Study of Depressive Symptoms in the Hispanic Community Health Study/Study of Latinos

---

Table of Contents

Description of Discovery and Replication Samples: Sampling, Genotyping, and Statistical Analyses

A. Hispanic Community Health Study/Study of Latinos (HCHS/SOL)

The Hispanic Community Health Study (HCHS)/Study of Latinos (SOL) is a community-based prospective cohort study of 16,415 self-identified Hispanic/Latino persons (aged 18-74 at screening) from randomly selected households in four U.S. field centers (Chicago, IL; Miami, FL; Bronx, NY; San Diego, CA) with baseline examination (2008 to 2011) and yearly follow-up by telephone for at least three years. A second clinical exam is currently underway. The HCHS/SOL cohort includes participants who self-identified as having Hispanic/Latino background, who reported being Central American (n=1,730), Cuban (n=2,348), Dominican (n=1,460), Mexican (n=6,471), Puerto-Rican (n=2,728), and South American (n=1,068). The goals of the HCHS/SOL are to describe the prevalence of risk and protective factors for chronic conditions (such as diabetes, pulmonary disease, and cardiovascular disease), and to quantify mortality and disease exacerbation over time. The baseline clinical examination [1] included comprehensive biological (e.g., anthropometrics, blood draw, oral glucose tolerance test, ankle brachial pressure index, electrocardiogram), behavioral (e.g. dietary intake, physical activity, overnight sleep exam, tobacco and alcohol use), and socio-demographic (e.g., socioeconomic status, migration history) assessments.

The sample design and cohort selection has been previously described [2]. Briefly, a stratified two-stage area probability sample of household addresses was selected in each of the four field centers. The first sampling stage selected census block groups, and the second stage selected households within each block group. Both stages oversampled certain strata to increase the likelihood that a selected address yielded a Hispanic/Latino household. Households were screened for eligibility, and the 45-74 age group was oversampled, consistent with the goal of examining chronic disease and mortality outcomes. The unequal probabilities of selection in the HCHS/SOL cohort are taken into account by including a trimmed and calibrated sampling weight as a covariate in the association tests.

HCHS/SOL subjects who consented to have their DNA extracted for genetic studies had blood samples sent to Illumina Microarray Services for genotyping on the Illumina SOL HCHS Custom 15041502 B3 array. This array comprised the Illumina Omni 2.5M array (HumanOmni2.5-8v1-1) and additional custom content selected for HCHS/SOL, including ancestry-informative markers, variants characteristic of Amerindian populations, known GWAS hits, and other candidate gene markers. Quality assurance/quality control (QA/QC) was performed by Illumina, LA Biomed, and the HCHS/SOL Genetic Analysis Center (GAC) according to established methods [3] to generate recommended SNP and sample-level quality filters. In brief, samples were checked for annotated versus genetic sex, gross chromosomal anomalies [4], call rates, batch effects, duplicate sample discordance, Mendelian errors, relatedness, and population structure. 12,803 unique study samples passed quality control with a missing call rate < 1% and was used for imputation and association testing. SNPs that passed the Illumina/LA Biomed assay failure indicator were further filtered if they deviated from Hardy-Weinberg equilibrium ($p<10^{-5}$ in meta-analysis of groups of individuals with both parents from the same country of origin), had duplicate probe discordance >2 in 291 sample pairs, had missing call rate >2%, or had >3 Mendelian errors in 1,343 trios or duos. A total of 2,232,944 SNPs passed both quality and informativeness filters (unduplicated on the array and polymorphic)

Genome-wide imputation was carried out on all 12,803 samples together using the 1000 Genomes Project phase 1 reference panel [5] and IMPUTE2 software [6 7]. Genotypes were first pre-phased with SHAPEIT2 (v2.r644) and then imputed with IMPUTE2 (v2.3.0). Only variants with at least two copies of the minor allele present in any of the four 1000 Genomes continental panels were imputed, yielding a total of 25,568,744 imputed variants. Overall imputation quality was assessed both by looking at the distribution of imputed quality metrics by different MAF levels and by examining results from the IMPUTE2 internal masking experiments (as some genotyped variants were “masked”, meaning removed from the imputation basis). Finally, association analysis

results were filtered according to the "effective minor allele count," defined as 2p(1-p)Nv, where p is the estimated MAF, N is the sample size, and v is the imputation measure "oevar," which is equal to the ratio of observed variance of imputed dosages to the expected binomial variance. For genotyped SNPs, oevar is set to 1.

The following approach was used to simultaneously characterize population structure and relatedness between individuals within sub-populations, in the presence of admixed individuals.

1. Estimate relatedness using KING-robust [8], which is robust to discrete population structure but not to admixture or departures from HWE within sub-populations.
2. Use PC-AiR[9] to find ancestry-representative principal components with the following steps:
   a) Partition the sample into a mutually unrelated set and the remaining (relatives of the unrelated set)
   b) Perform standard principal components analysis (PCA) on the set of unrelated individuals
   c) Predict sample eigenvectors for the set of related individuals based on genetic similarity
3. Re-estimate relatedness using PC-Relate [10], which uses sample eigenvectors to provide unbiased kinship coefficients in the presence of population structure, admixture and HWE departures.
4. Repeat steps 2-3 to obtain final sets of sample eigenvectors and kinship coefficients.

This procedure identified 19 individuals with primarily East Asian ancestry, who were excluded from analysis and the above procedure was repeated for the remaining 12,784 samples.

To account for the possibility that current use of antidepressant medications might affect depressive symptoms scores, we applied an adjustment algorithm to increase the scores of medication users. This algorithm was used in a previous GWAS of depressive symptoms [11] and was similar to an algorithm used to adjust blood pressure for persons on antihypertensive medications [12]. Antidepressant medication use was determined by pill bottles brought by the participant to the baseline interview, which were scanned using UPC codes. This algorithm assumed that: (1) the depressive symptoms score of a respondent taking these antidepressant medications is *lower* (i.e., indicating fewer symptoms) than would be expected if the respondent were not taking these medications (thus, we assume that the medications are effective in reducing symptoms); and (2) respondents with high depressive symptoms scores, on average, respond less to these medications than respondents with lower depressive symptoms scores. The algorithm therefore replaced the depressive symptoms score of respondents on antidepressant medication (n=824) with the mean depressive symptoms score of all respondents taking medication that had the same or a higher depressive symptoms score. For example, a medication user with an observed depressive score of 10 would have a revised score of 16.749 (derived by taking the average depressive symptoms score of medication users with a depressive symptom score value of 10 or greater). Depressive symptoms scores for medication users were increased by 6.37 points on average above the raw score (raw scores ranged from 0-30).

Details regarding the distribution of covariates in the total sample and stratified by gender and psychiatric medication use are included below.

Table 1. Distribution of covariates in the total sample and stratified by gender and psychiatric medication users

	Total Sample	Sex		Medication Use	
		Males	Females	User	Non-User
n	12310	5046	7264	824	11486
Age (mean, sd)	46 (14)	45 (14)	47 (14)	53 (11)	46 (14)
Male	5046 (41%)	-	-	214 (26%)	4832 (42%)
Medication use	824(7%)	214(4%)	610(8%)	-	-
US born	2194 (18%)	980(19%)	1214(17%)	153 (19%)	2041 (18%)
Education					
At least high school	3146 (26%)	1400(28%)	1746(24%)	186 (23%)	2960 (26%)
No high school diploma or GED	4518 (37%)	1789(35%)	2729(38%)	341 (41%)	4177 (36%)
Greater than high school	3255 (26%)	1237(25%)	2018(28%)	215 (26%)	3040 (26%)
Bachelors degree	1008 (8%)	451(9%)	557(8%)	54 (7%)	954 (8%)
Masters/professional/ doctorate degree	383 (3%)	169(3%)	214(3%)	28 (3%)	355 (3%)
Genetic Group					
Central American	1371 (11%)	555(11%)	816(11%)	56 (7%)	1315 (11%)
South American	895 (7%)	359(7%)	536(7%)	29 (4%)	866 (8%)
Mexican	4580 (37%)	1802(36%)	2778(38%)	236 (29%)	4344 (38%)
Puerto Rican	2141 (17%)	900(18%)	1241(17%)	258 (31%)	1883 (16%)
Cuban	2219 (18%)	1046(21%)	1173(16%)	174 (21%)	2045 (18%)
Dominican	1104 (9%)	384(8%)	720(10%)	71 (9%)	1033 (9%)

Cell entries are N (%) unless otherwise denoted.

B. Women's Health Initiative (WHI) SNP Health Association Resource (SHARe)

As described elsewhere [13 14] (www.whi.org), the WHI consists of an observational study (WHI-OS) and randomized clinical trial (WHI-CT). The WHI-OS has prospectively followed 93,676 postmenopausal women ages 50-79 recruited from 40 clinical centers in the United States between October 1 1993 and December 31 1998. The WHI-CT enrolled 68,132 postmenopausal women of the same age and between the same time period to participate in one of three prevention trials: (1) hormone therapy; (2) dietary modification; and (3) calcium/vitamin D. We analyzed data from 3,352 Hispanic women who were genotyped as part of the WHI SNP Health Association Resource (SHARe), a sub-study of minority women in WHI. These women consented to be included in studies for general research use and thus had their data included in the database of Genotypes and Phenotypes (dbGaP).

All participants were genotyped using the Affymetrix 6.0 chip designed to human genome build 36. Genotyping, on all samples plus 2% blinded duplicates, was performed at Affymetrix, Inc., Santa Clara, CA. A total of 709,042 SNPs passed pre-imputation filters. Data cleaning and harmonization were performed at the Fred Hutchinson Cancer Research Center (FHCRC) in Seattle, WA. As described elsewhere [15], the WHI GARNET Coordinating Center (www.garnetstudy.org) imputed additional SNPs using the 1000 Genomes reference panel build 37 (release December 2010 interim) and BEAGLE software version 3.3.1 [16]. SNPs were selected for imputation based on mapping to build 37 and meeting several quality filters. Specifically, SNPs with low concordance rates (<98% ascertained from duplicate samples), and low call rates (<95%) were excluded from imputation and SNPs with minor allele frequency (MAF) of ≥ 1% and Hardy-Weinberg

equilibrium p-values > 0.0001 were included. A combined panel of Asian, European, African, and American samples was used to impute the Hispanic/Latina sample. Allele dosages (the probability of each of the three genotypes, reflecting the level of certainty in the genotype prediction) were imputed for autosomes (7,500,448 imputed SNPs) and the X chromosome.

In the analysis of WHI, we adjusted for the following covariates, measured at baseline: age (ages 50-59-referent; ages 60-69; ages 70-79), income (1=less than 19,000-referent; 2=20,000-49,000; 3=50,000 and above; 4=missing), education (1=less than high school-referent; 2=high school/vocational technical training; 3=some college or Associates degree; 4=college degree; 5=graduate school or degree; 6=missing), marital status (1=never married-referent; 2=divorced/separated; 3=widowed; 4=married/married like relationship; 5=missing), and four principal components generated by the WHI GARNET Coordinating Center using EIGENSTRAT [17] to adjust for population structure [15].

C. Multi-Ethnic Study of Atherosclerosis (MESA)

The MESA is a multicenter prospective cohort study initiated to study the development of subclinical cardiovascular disease (CVD). A total of 6,814 women and men between the age of 45 and 84 year were recruited for the first examination between 2000 and 2002. Participants were recruited in six US cities (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angele County, CA; Norther Manhattan, NY; and St. Paul, MN). Those with a history of CVD (defined as physician-diagnosed myocardial infarction, angina, heart failure, stroke, transient ischemic attack or history of invasive procedure for CVD) were excluded from participation. 38% are of European ancestry, 28% African-American, 22% Hispanic, and 12% Asian, predominantly of Chinese descent. This study was approved by the IRB of each study site, and written informed consent was obtained from all participants [18]. The manuscript utilizes data from Hispanic-American MESA participants. A total of 1500 MESA Hispanic-Americans were used in this analysis.

All participants were genotyped on the Affymetrix Genome-Wide Human SNP Array 6.0 (Affymetrix, Santa Clara, CA, USA) at the Affymetrix Research Services Lab. 6880 samples passed initial genotyping QC. African American samples were genotyped at the Broad Institute of Harvard and MIT as part of the CARe project. Affymetrix performed wet lab hybridization assay, and plate-based genotype calling using Birdseed v2. Sample QC was based on call rates and contrast QC (cQC) statistics. Broad performed similar QC for CARe sample. Additional sample and SNP QC were carried out at University of Virginia, including sample call rate, sample cQC, and sample heterozygosity by race at the sample level; Outlier plates checking by call rate, median cQC or heterozygosity at plate level. Four samples were removed due to low call rate (<95%). Cryptic sample duplicates or unresolved cryptic duplicates were dropped. Unresolved gender mismatches were also dropped. At the SNP level, we excluded monomorphic SNPs across all samples; SNPs with missing Rate was > 5% or observed heterozygosity > 53% were also excluded. Additional genotypes were imputed to the 1000 Genomes Phase I integrated variant set (NCBI build 37 / hg19) separately in each ethnic group using the program IMPUTE2. We used data freezes from 23 Nov 2010 (low-coverage whole-genome) and 21 May 2011 (high-coverage exome), phased haplotypes released March 2012 (v3), and phased haplotypes for 1,092 individuals and 39+ million variants. All imputed and genotyped SNPs were aligned to the '+' strand of the human genome reference sequence (NCBI Build 37).

In the analysis of MESA, we adjusted for the following covariates measured at baseline: gender (1=male, 2=female), age (treated as continuous), education (1=less than high school-referent; 2=high school/vocational technical training; 3=some college or Associates degree; 4=college degree; 5=graduate school or degree; 6=missing), study site (3=WFU; 8=UCLA; 4=COL;6=UMN;5=JHU;7=NWU), antidepressant medication (non-tricyclic antidepressants other than MAOI 1=yes 0=no) and three principal components generated to adjust for population structure .

D. Army Study To Assess Risk and Resilience in Service members (Army STARRS)

Army STARRS includes New Soldier Study (NSS) and Pre/Post Deployment Study (PPDS). Detailed information about the design and conduct of Army STARRS is available in another publication. [19]. The recruitment, consent, and data protection procedures were approved by the Human Subjects Committees of the Uniformed Services University of the Health Sciences for the Henry M. Jackson Foundation (the primary grantee), the Institute for Social Research at the University of Michigan (the organization collecting the data), and all other collaborating organizations.

The New Soldier Study was carried out among new soldiers at the start of their basic training at one of three Army Installations (Fort Benning, GA; Fort Jackson, SC; and Fort Leonard Wood, MO) between April 2011 and November 2012. Recruitment began by selecting a weekly sample of 200–300 new soldiers in each installation to attend a study overview and informed consent presentation for the study. Army STARRS staff worked closely with Army coordinators to assure that these samples were representative of all new soldiers in each weekly cohort. The overview and informed consent presentation explained study purposes, confidentiality, emphasized that participation was voluntary, and answered all questions before seeking written informed consent to (i) complete a self-administered questionnaire (SAQ), (ii) link administrative records to SAQ responses, and (iii) participate in future data collections. Identifying information (e.g., name, SSN) was collected from consenting respondents and kept in a separate secure file. Soldiers were also asked to provide an optional blood sample for research purposes, which was specified to include genetic analysis as described in this report. Of 39,784 NSS respondents who completed the SAQ, 33,088 (83.2%) provided blood samples. As these samples were accruing, it was decided to pursue genotyping from among approximately the first half (N = 17,868) of the cohort that was available at that time; we refer to this component of the study as NSS1. The first 17,868 eligible respondents were purposively subsampled for genotyping as follows: (1) respondents with DSM-IV lifetime disorders of principal interest (major depressive disorder, generalized anxiety disorder, panic disorder, PTSD, suicide attempt, other deliberate self-harm) sampled at 100% [N = 4,024]; and (2) a subset of respondents with none of the disorders of principal interest, stratum-matched on sex, service type (Regular Army vs. Guard/Reserve), and childhood adversity quartile (detailed description available on request from the authors) [N = 3,975]. In total this yielded 7,999 NSS respondents with eligible SAQ responses genotyped with the Illumina OmniExpress Chip (NSS1). When the remaining half (N = 15,220) of the cohort collection was completed, it was decided to select a highly informative subset (i.e., all cases of PTSD and suicide attempt, and a set of controls matched to these cases as described above for NSS1) as a potential replication sample. This yielded an additional 2,835 NSS respondents genotyped with the Illumina customized PsychChip; we refer to this component of the study as NSS2.

The Pre/Post Deployment Study is a multi-wave panel survey that collected baseline data (T0; self-administered questionnaire [SAQ]) from US Army soldiers in three Brigade Combat Teams (BCTs) during the first quarter of 2012, within approximately six weeks of their deployment to Afghanistan. Baseline PPDS respondents were additionally asked for consent to provide blood samples for genetic and other studies, to link their Army and DoD administrative records to their survey responses, and to participate in future assessments. At the baseline (T0), a total of 9,949 Soldiers were present for duty in the 3 BCTs. Of these, a total of 9,488 (95.3%) consented to participate in the survey with 8,558 (86.0%) providing complete T0 survey responses and consent to link their survey responses to their administrative records. Of these, 7,336 PPDS soldiers with eligible SAQ responses whose DNA was genotyped for GWAS (using the same microarray as for NSS1) are included here.

Blood for DNA (approximately 8 ml drawn in a 10 ml EDTA-containing tube) was drawn from consenting soldiers in all studies. Whole blood samples were shipped with gel cool packs to the study biorepository at Rutgers University Cell & DNA Repository (RUCDR), where they were frozen for later DNA extraction using standard methods. NSS1 and PPDS samples were genotyped using the Illumina OmniExpress + Exome array with additional custom content. This array contains 730,000 tag SNPS with minor allele frequency (MAF) typically > 5% and another 237,000 predicted-functional exonic markers. NSS2 samples were genotyped on the Ilumina PsychChip. This array is currently being used by the PGC to genotype more than 100,000 individuals across a range of psychiatric disorders. PsychChip is built on a 250,000 GWAS tag-SNP backbone, with 250,000 exonic rare variants and ~50,000 markers derived partly from prior neuropsychiatric studies. Samples

were genotyped by RUCDR Infinite Biologics using the appropriate Illumina (OmniExpress or PsychChip) microarray protocol and calls were made using GenomeStudio Software (Illumina, Inc.).

Pre-imputation quality control (QC) of genotype data was done with standard protocols as described elsewhere [20]. Genotype imputation was performed with a 2-step pre-phasing/imputation approach. We used SHAPEIT [21] for the pre-phasing and IMPUTE2 [22] for imputation, with a reference panel from 1000 Genomes Project[5] (August 2012 phase 1 integrated release; 2,186 phased haplotypes with 40,318,245 variants). We removed SNPs that were not present in the 1000 Genomes Project reference panel, had non-matching alleles to 1000 Genome Project reference, or with ambiguous, unresolvable alleles (AT/GC SNPs with minor allele frequency [MAF] > 0.1). A total of 664,457 SNPs for the Illumina OmniExpress array and 360,704 for the Illumina PsychChip entered the imputation.

We assigned our study samples into distinct population groups based on PCs derived from the study samples combined with the HapMap3 samples. We used an iterative process to extract study samples to be assigned into groups with ancestral backgrounds close to the major continental/admixed reference samples from HapMap3. We defined four major population groups in our study samples: European Americans, African Americans, Latino Americans, and East Asian Americans. The Latino American samples were included in the current study. We performed PCA within the population group using only the study samples to obtain the top PCs for statistical analysis.

We adjusted for the following covariates in the current analysis: gender, age, endorsed medication for mental health problems in the past year (1=yes, 0=no or missing) and 10 principal components generated to adjust for population structure. The 3 study components (NSS1, NSS2 and PPDS) were analyzed separately.

The SNPs rs34208798 and rs2004237 were imputed in Army STARRS with imputation info scores of 0.97-1.08 and 0.87-0.94 respectively.

Description of Depressive Symptoms in Each Sample

Table II below summarizes the individual items used to capture depressive symptoms across each of the replication studies. The table is organized by the HCHS/SOL indicators to show where similar items were assessed across each replication study.

WHI

Depressive symptoms were assessed using the 6-item version of the CES-D. Participants were asked to indicate how often in the past week, did they: (1) feel depressed; (2) have sleep that was restless; (3) enjoy life; (4) have crying spells; (5) feel sad; (6) feel people disliked you. The 6-item CES-D has been found to correlate with the full 20-item CES-D (r=0.88) [23] in participants of the Systolic Hypertension in the Elderly Program (SHEP)[24], a population of elderly women similar to that of the WHI. Response options were: 1=rarely or none of the time (less than 1 day); 2=some or a little of the time (1-2 days); 3=occasionally or a moderate amount of time (3-4 days); 4=all the time (5-7 days). Depressive symptom scores were calculated by summing across the items.

MESA

For the replication in MESA, depressive symptoms were assessed using the 20-item version of the CES-D [25]. Participants were asked how often in the past week they: (1) were bothered by things that usually don't bother me; (2) did not feel like eating/appetite was poor; (3) felt that I could not shake off the blues even with help from my family; (4) felt I was just as good as other people; (5) had trouble keeping my mind on what I was doing; (6) felt depressed; (7)felt everything I did was an effort; (8) felt hopeful about the future; (9) thought my life had been a failure; (10) felt fearful; (11) sleep was restless; (12) was happy; (13) talked less than usual; (14) felt lonely; (15) people were unfriendly; (16) enjoyed life; (17) had crying spells; (18) felt sad; (19) felt people disliked me; (20) could not get going. Responses ranged from 0=rarely or none of the time (less than 1 day) to 3=all the time (5-7 days); items (4), (8), (12), and (16) were reverse scored. For participants with 5 or fewer missing items, depressive scores were computed by summing across the completed items, dividing by the total number of complete answers, and multiplying by 20.

Army STARRS

Depressive symptoms were measured with a four-item Composite International Diagnostic Interview Screening Scale (CIDI-SC) for major depressive episode (MDE), which included the items: (1) feeling sad or depressed; (2) down about how things are going; (3) little or no pleasure in things; (4) feeling down on yourself or worthless in the past 30 days [26]. Responses ranged from 4=all the time to 0=none of the time. Depressive symptom scores were calculated as the sum of the four items (range 0-16).

Table 2. Summary of depressive symptom indicators used across each study			
HCHS/SOL	**MESA**	**Army STARRS**	**WHI**
I was bothered by things that usually don't bother me.	**		
I had trouble keeping my mind on what I was doing.	**		
I felt depressed.	**	Felt sad or depressed	**
I felt that everything I did was an effort.	**		
I felt hopeful about the future.	**	Felt down on yourself, worthless	
I felt fearful.	**		
My sleep was restless.	**		**
I was happy.	**		
I felt lonely.	**		
I could not "get going."	**	Little or no interest or pleasure in things	
	I enjoyed life.		I enjoyed life.
	I had crying spells.		I had crying spells.
	I felt sad.	Down about how things are going	I felt sad.
	I felt that people disliked me.		I felt that people disliked me.
	I felt that I could not shake off the blues even with help from my family.		
	I did not feel like eating; my appetite was poor		
	I felt that I was just as good as other people.		
	I thought my life had been a failure.		
	I talked less than usual.		
	People were unfriendly.		
** denotes item worded identically to the HCHS/SOL			

Supplemental Tables

Supplemental Table 1: Results of genome-wide complex trait analysis

	Original scores			Accounting for medication use			Medication users removed		
Depressive symptoms score	N	V(G)/Vp*100 (95% CI)	p	N	V(G)/Vp*100 (95% CI)	p	N	V(G)/Vp*100 (95% CI)	p
All individuals	12310	6.4 (1.6, 11.1)	0.002	12310	6.3 (1.6, 11.1)	0.002	11486	6.9 (2.3, 12)	0.002
Unrelated individuals	9992	4 (0, 10.1)	0.082	9992	2.9 (0, 8.9)	0.153	9396	3.8 (0, 10.3)	0.104

V(G)/Vp*100 = SNP heritability estimate (h^2_{SNP})*100. The phenotype was treated as continuous. Models adjusted for sex, age, education (5-levels), principal components, study center, and sampling weights, and included random effects for the design variables kinship, household, and block unit, the three study design variables. P-values were calculated using the likelihood ratio test. For completeness, we show these results for both all individuals (included in the GWAS) and genetically unrelated individuals. Genetically unrelated individuals were a random subset of individuals with pairwise estimated kinship coefficients less than $2^{-11/12}$.

Supplemental Table 2: Genome-wide association study (GWAS) results for the top loci ($p<1x10^{-5}$) with the depressive symptom score, after adjusting for medication use

SNP	CHR	position	alleleA	alleleB	Minor Allele	MAF	geno	n	info	Beta	SE	pval	effN
12:102245668:C:T	12	102245668	C	T	T	0.01	0	12310	0.981	-2.024	0.39	2.07E-07	282.7926
12:102237322:G:A	12	102237322	G	A	A	0.01	0	12310	0.977	-2.029	0.392	2.23E-07	280.8041
12:102238063:GA:G	12	102238063	GA	G	G	0.01	0	12310	0.98	-2.017	0.392	2.65E-07	279.5283
rs72662446	8	59113186	C	T	T	0.03	2	12309	1	-1.138	0.232	9.04E-07	765.584
rs56712382	5	39209149	G	GCA	GCA	0.28	0	12310	0.893	0.487	0.099	9.75E-07	4761.03
rs9599044	13	66494976	T	A	A	0.03	0	12310	0.961	1.242	0.254	1.00E-06	631.3256
rs5841036	20	24502210	T	TG	T	0.02	0	12310	0.9	1.546	0.317	1.04E-06	408.1463
7:66564018:AT:A	7	66564018	AT	A	A	0.21	0	12310	0.953	-0.508	0.104	1.11E-06	3952.047
rs10268701	7	66515528	C	G	G	0.19	0	12310	0.995	-0.509	0.105	1.12E-06	3856.418
rs7198462	16	77395589	T	C	C	0.01	0	12310	0.972	-2.036	0.419	1.15E-06	243.704
rs11761677	7	66513614	G	A	A	0.19	0	12310	0.999	-0.510	0.105	1.16E-06	3808.594
rs10228308	7	66515614	T	C	C	0.19	2	12310	1	-0.509	0.105	1.24E-06	3799.051
rs10238245	7	66515394	G	A	A	0.19	0	12310	1	-0.509	0.105	1.26E-06	3799.227
rs12198471	6	6906545	C	T	T	0.2	2	12310	1	0.498	0.103	1.29E-06	3899.423
rs138895464	11	113660083	A	T	T	0.01	0	12309	0.995	-1.764	0.365	1.31E-06	327.4409
rs10234407	7	66514708	G	A	A	0.19	0	12310	1	-0.506	0.105	1.44E-06	3803.627
rs34208798	7	66518851	G	A	A	0.19	0	12310	0.999	-0.507	0.105	1.47E-06	3764.943
rs55777322	7	66559640	T	G	G	0.19	0	12310	0.986	-0.511	0.106	1.48E-06	3754.231
rs10242790	7	66516641	A	G	A	0.19	0	12310	0.999	0.504	0.105	1.61E-06	3806.535
rs117254441	16	52657128	T	C	T	0.03	0	12310	0.842	1.128	0.236	1.76E-06	720.4923
rs7808645	7	66514516	A	T	T	0.19	0	12310	0.991	-0.503	0.106	2.06E-06	3760.58
rs2242643	14	80286394	T	C	C	0.46	0	12309	0.998	-0.380	0.08	2.18E-06	6118.67
rs113737600	7	66615118	C	A	A	0.16	0	12310	0.993	-0.526	0.111	2.21E-06	3342.016
rs373861332	7	66557326	T	G	G	0.19	0	12310	0.999	-0.496	0.105	2.35E-06	3794.917
rs1462245	11	38285992	A	C	A	0.09	2	12310	1	0.729	0.154	2.35E-06	1981.208
rs12333596	7	66551407	G	A	A	0.19	0	12310	0.999	-0.493	0.105	2.48E-06	3820.43
rs17144784	7	66551370	G	A	A	0.19	0	12310	0.999	-0.493	0.105	2.48E-06	3820.429
rs10231655	7	66552282	A	G	G	0.19	0	12310	0.999	-0.493	0.105	2.48E-06	3820.455
rs28484969	7	66555347	G	T	T	0.19	0	12310	0.999	-0.493	0.105	2.51E-06	3820.571
rs10226634	7	66550307	T	C	C	0.19	0	12310	0.999	-0.493	0.105	2.52E-06	3820.544
rs71563157	7	66555846	G	A	A	0.19	0	12310	1	-0.492	0.105	2.56E-06	3820.824
rs2711913	7	66557020	C	G	G	0.19	0	12310	0.999	-0.492	0.105	2.56E-06	3820.843

rs66859603	7	66557148	C	T	T	0.19	0	12310	0.999	-0.492	0.105	2.56E-06	3820.846
rs55994185	7	66557950	G	A	A	0.19	0	12310	0.999	-0.492	0.105	2.57E-06	3820.861
rs55974240	7	66558071	C	T	T	0.19	0	12310	0.999	-0.492	0.105	2.57E-06	3820.864
rs10228932	7	66561217	C	A	A	0.19	0	12310	0.999	-0.492	0.105	2.59E-06	3820.941
rs7787409	7	85056967	T	C	T	0.04	0	12310	0.964	1.017	0.216	2.63E-06	872.4793
rs11761516	7	66525513	T	C	T	0.19	0	12310	0.997	0.492	0.105	2.65E-06	3819.067
rs7782407	7	66546243	A	G	G	0.19	0	12310	0.999	-0.491	0.105	2.74E-06	3808.32
rs6957569	7	66562441	G	A	A	0.19	0	12310	0.999	-0.490	0.105	2.81E-06	3822.016
rs62123284	19	8214984	A	G	G	0.31	2	12310	1	0.407	0.087	2.83E-06	5268.421
rs13222968	7	66533077	T	C	C	0.19	0	12310	1	-0.490	0.105	2.84E-06	3827.687
rs7791271	7	66602986	C	T	T	0.19	0	12310	0.999	-0.491	0.105	2.84E-06	3810.871
rs34813948	7	66529741	C	G	G	0.19	0	12310	1	-0.489	0.105	2.87E-06	3827.67
rs10228812	7	66561114	C	T	T	0.2	0	12310	0.998	-0.482	0.103	2.87E-06	3934.739
rs112483740	7	66528519	C	CAAAT	CAAAT	0.19	0	12310	0.999	-0.489	0.105	2.89E-06	3828.914
rs55719516	8	59114301	T	C	C	0.04	0	12309	0.999	-1.042	0.223	2.89E-06	839.014
rs7807231	7	66543514	T	A	A	0.19	0	12310	1	-0.489	0.105	2.96E-06	3831.201
rs10252479	7	66541889	C	A	A	0.19	0	12310	1	-0.489	0.105	2.96E-06	3831.202
rs10281398	7	66542135	G	A	A	0.19	0	12310	1	-0.489	0.105	2.96E-06	3831.202
rs7794380	7	66545725	G	C	C	0.19	0	12310	1	-0.489	0.105	2.96E-06	3831.2
rs10280810	7	66541706	G	A	A	0.19	0	12310	1	-0.489	0.105	2.96E-06	3831.202
rs12334126	7	66539772	G	A	A	0.19	0	12310	1	-0.489	0.105	2.96E-06	3831.203
rs2711923	7	66546656	G	C	C	0.19	0	12310	1	-0.489	0.105	2.97E-06	3831.282
rs11771640	7	66547296	T	G	G	0.19	0	12310	1	-0.489	0.105	2.97E-06	3831.364
rs5791224	11	38286939	G	GA	G	0.09	0	12310	1	0.722	0.155	2.97E-06	1980.174
rs11348807	7	66549247	TA	T	T	0.19	0	12310	1	-0.488	0.105	2.98E-06	3831.435
rs59852863	7	66546207	CTTTT	C	C	0.2	0	12310	0.993	-0.485	0.104	3.00E-06	3905.257
rs67178340	7	66538797	C	T	T	0.19	0	12310	0.999	-0.488	0.105	3.02E-06	3831.728
rs71563154	7	66538714	T	C	C	0.19	0	12310	0.999	-0.488	0.105	3.03E-06	3831.78
rs71563153	7	66538688	G	T	T	0.19	0	12310	0.999	-0.488	0.105	3.03E-06	3831.796
rs10273674	7	66517049	C	T	T	0.19	0	12310	0.999	-0.489	0.105	3.04E-06	3816.574
rs56738524	8	8420053	A	G	A	0.34	0	12309	0.995	-0.398	0.085	3.04E-06	5512.177
rs147890196	11	9249517	G	A	A	0.04	0	12310	0.992	-0.974	0.209	3.04E-06	864.9068
rs3813771	19	8213590	C	T	T	0.31	0	12310	0.999	0.407	0.087	3.05E-06	5246.758
rs10611601	7	70044230	TAA	T	TAA	0.43	0	12310	0.849	-0.411	0.088	3.06E-06	5082.999
rs1585555	11	38287507	C	T	C	0.09	0	12310	1	0.722	0.155	3.07E-06	1978.353
rs59540627	7	66528654	G	C	C	0.19	0	12310	0.999	-0.488	0.105	3.08E-06	3831.159
rs1599564	11	38288114	C	A	C	0.09	0	12310	0.999	0.721	0.155	3.09E-06	1979.385

rs2292143	5	168213007	G	A	A	0.16	2	12310	1	-0.512	0.11	3.12E-06	3339.987
rs67737819	7	66566448	G	A	A	0.19	0	12310	0.999	-0.489	0.105	3.14E-06	3807.467
rs10269571	7	66516151	C	T	T	0.19	0	12310	1	-0.488	0.105	3.15E-06	3816.516
rs55704136	7	66589409	G	C	C	0.19	0	12310	0.999	-0.487	0.104	3.18E-06	3834.8
rs10249716	7	66523521	G	T	T	0.19	0	12310	0.998	-0.487	0.105	3.26E-06	3830.591
rs11524606	7	66522546	C	T	T	0.19	0	12310	0.999	-0.487	0.105	3.28E-06	3827.413
rs35913158	7	66584841	C	T	T	0.19	0	12310	0.999	-0.488	0.105	3.32E-06	3796.464
rs28857233	7	66528050	T	A	A	0.2	0	12310	0.984	-0.487	0.105	3.36E-06	3870.664
rs17144710	7	66584459	G	T	G	0.19	0	12310	0.999	0.486	0.105	3.40E-06	3821.136
rs58942690	7	66538918	C	A	A	0.19	0	12310	0.997	-0.486	0.105	3.40E-06	3841.92
rs12698557	7	66521471	T	C	C	0.19	0	12310	0.999	-0.486	0.105	3.40E-06	3827.352
rs10825348	10	56303614	T	A	A	0.41	0	12310	0.993	0.384	0.083	3.42E-06	5946.532
rs7800350	7	66567698	G	T	T	0.19	0	12310	0.999	-0.485	0.105	3.43E-06	3833.37
rs151216651	1	237250656	T	TCTC	TCTC	0.01	0	12310	0.996	-1.741	0.375	3.48E-06	294.181
rs6975866	7	66543980	C	T	C	0.19	0	12310	0.999	0.485	0.105	3.52E-06	3829.657
rs55731089	7	66520438	C	T	T	0.19	0	12310	0.999	-0.485	0.105	3.53E-06	3827.315
rs58756282	7	66584920	C	T	T	0.19	0	12310	1	-0.485	0.105	3.59E-06	3822.248
rs10224763	7	66586221	A	G	G	0.19	0	12310	1	-0.485	0.105	3.59E-06	3822.245
rs10249587	7	66523392	G	A	A	0.19	0	12310	0.999	-0.485	0.105	3.61E-06	3831.745
rs2049831	14	80289134	G	A	A	0.46	0	12309	0.998	-0.372	0.08	3.61E-06	6121.819
rs10925309	1	237250487	G	C	C	0.01	0	12310	0.995	-1.739	0.375	3.62E-06	294.293
rs2154265	10	56305290	T	C	C	0.41	0	12310	0.988	0.383	0.083	3.62E-06	5974.417
rs11314136	7	66519689	AT	A	A	0.19	0	12310	0.999	-0.485	0.105	3.64E-06	3827.223
rs1445962	5	50300969	T	G	G	0.03	0	12309	0.997	-1.219	0.263	3.65E-06	644.569
rs7793589	7	66608855	G	T	T	0.18	0	12310	0.997	-0.496	0.107	3.72E-06	3608.105
rs78316461	7	66513067	G	A	A	0.19	0	12310	0.999	-0.484	0.105	3.73E-06	3827.203
rs10259711	7	66518946	C	T	T	0.19	0	12310	0.999	-0.484	0.105	3.74E-06	3827.171
rs34157075	7	66512317	A	C	C	0.19	0	12310	0.999	-0.484	0.105	3.74E-06	3827.298
rs12154876	7	66563135	A	G	G	0.19	0	12310	0.999	-0.486	0.105	3.75E-06	3790.52
rs17438468	2	193203685	C	T	C	0.02	0	12310	0.97	1.339	0.29	3.79E-06	481.81
rs2242648	14	80297210	G	C	C	0.46	0	12309	0.999	-0.371	0.08	3.84E-06	6119.945
rs6973836	7	66569208	G	A	A	0.19	0	12310	0.999	-0.484	0.105	3.86E-06	3809.351
rs79295862	5	50247859	T	C	C	0.02	0	12309	0.984	-1.523	0.33	3.87E-06	408.79
rs7783157	7	66574420	A	C	C	0.19	0	12310	0.998	-0.484	0.105	3.96E-06	3807.082
rs13243892	7	66576213	C	T	T	0.19	0	12310	0.999	-0.483	0.105	4.00E-06	3810.877
rs143925771	7	66578612	C	T	T	0.19	0	12310	0.999	-0.484	0.105	4.09E-06	3782.952
rs71535636	7	66512581	T	C	C	0.19	0	12310	0.999	-0.482	0.105	4.11E-06	3824.649

rs28465142	7	66611347	A	C	C	0.18	0	12310	0.999	-0.491	0.107	4.12E-06	3640.877
rs2140564	7	66590824	G	C	C	0.19	0	12310	0.999	-0.484	0.105	4.17E-06	3777.544
rs2960970	7	66574209	C	T	T	0.19	0	12310	1	-0.481	0.104	4.20E-06	3835.197
rs3857691	7	66608420	C	G	G	0.18	0	12310	1	-0.489	0.106	4.24E-06	3666.733
rs59247139	7	66574425	C	T	T	0.19	0	12310	0.999	-0.481	0.105	4.29E-06	3832.919
rs7099825	10	56304265	A	G	G	0.41	2	12310	1	0.379	0.082	4.32E-06	5959.839
rs73109514	5	50306261	G	C	C	0.03	0	12309	0.994	-1.222	0.266	4.39E-06	631.39
rs10262781	7	66620160	C	T	T	0.18	0	12310	1	-0.489	0.106	4.39E-06	3664.474
rs7350002	7	66620603	G	A	A	0.18	0	12310	1	-0.489	0.106	4.39E-06	3664.473
rs7792212	7	66621143	G	A	A	0.18	0	12310	1	-0.489	0.106	4.40E-06	3664.471
rs11004372	10	56304691	A	G	G	0.41	0	12310	0.995	0.380	0.083	4.40E-06	5958.309
rs35122750	7	66607147	A	G	G	0.18	0	12310	0.999	-0.490	0.107	4.43E-06	3635.922
rs9690120	7	66618358	G	A	A	0.18	0	12310	0.999	-0.489	0.106	4.43E-06	3664.976
rs10825349	10	56303722	A	G	G	0.41	0	12310	0.995	0.380	0.083	4.49E-06	5942.501
rs2004237	19	8209194	T	C	C	0.31	0	12310	0.995	0.399	0.087	4.49E-06	5282.771
rs6978918	7	66614462	T	C	C	0.18	2	12310	1	-0.488	0.106	4.53E-06	3667.336
rs10925310	1	237251005	T	C	C	0.01	2	12310	1	-1.693	0.37	4.64E-06	302.197
rs2687052	7	66621824	A	G	G	0.18	0	12310	0.998	-0.489	0.107	4.70E-06	3644.115
rs7809649	7	66602947	A	G	G	0.19	0	12310	0.998	-0.482	0.105	4.73E-06	3767.027
rs27276	5	50243725	G	A	G	0.02	0	12309	0.996	1.402	0.307	5.06E-06	459.655
rs113086330	5	50230664	C	T	T	0.02	0	12309	0.995	-1.472	0.323	5.11E-06	422.258
rs28888140	7	66593134	T	C	C	0.19	0	12310	1	-0.477	0.105	5.16E-06	3819.527
rs10274580	7	66592378	C	A	A	0.19	0	12310	1	-0.477	0.105	5.17E-06	3819.475
rs60910884	7	66598251	C	T	T	0.19	0	12310	1	-0.477	0.105	5.17E-06	3819.469
rs10233183	7	66597207	C	T	T	0.19	0	12310	1	-0.477	0.105	5.17E-06	3819.469
rs149883819	7	66600352	C	CA	CA	0.19	0	12310	1	-0.477	0.105	5.17E-06	3819.421
rs10244331	7	66622569	G	A	A	0.18	0	12310	0.999	-0.485	0.106	5.20E-06	3664.322
rs6603149	19	8213231	A	G	G	0.38	2	12310	1	0.376	0.083	5.59E-06	5803.442
rs1506452	1	71781585	A	G	G	0.32	2	12310	1	0.397	0.088	5.70E-06	5340.521
rs182384587	-	16517523	G	T	T	0.02	0	12296	0.883	-1.319	0.291	5.72E-06	292.801
rs12751629	1	71793221	C	A	C	0.32	0	12310	1	-0.397	0.088	5.76E-06	5340.263
rs58448907	7	66595583	A	G	G	0.19	0	12310	0.999	-0.477	0.105	5.77E-06	3776.882
rs200905081	7	66610751	G	GT	GT	0.18	0	12310	0.998	-0.485	0.107	5.94E-06	3612.222
rs77219363	20	24489072	C	CCAGGCTG ATCT	C	0.03	0	12310	0.814	1.119	0.247	5.96E-06	663.5196
rs7793104	7	66621061	C	T	T	0.18	0	12310	0.999	-0.483	0.107	6.15E-06	3619.882
rs7776751	7	66608570	A	G	G	0.18	0	12310	0.999	-0.483	0.107	6.21E-06	3619.908
rs34457100	5	50170509	T	TA	T	0.02	0	12309	0.978	1.485	0.329	6.28E-06	410.341

rs144669467	3	98857716	CT	C	CT	0.19	0	12310	0.987	-0.465	0.103	6.32E-06	3682.868
rs7003790	8	59105992	C	T	T	0.03	0	12309	0.997	-1.024	0.227	6.33E-06	811.622
rs8127353	21	44076975	G	T	T	0.02	2	12309	1	-1.317	0.292	6.35E-06	479.2867
rs3729908	16	24231248	T	C	T	0.07	0	12310	0.949	0.721	0.16	6.56E-06	1587.213
rs80269587	7	109709947	C	T	C	0.01	0	12310	0.94	1.747	0.388	6.70E-06	264.3286
rs12561925	1	71813142	C	G	G	0.32	0	12310	0.994	0.394	0.088	6.75E-06	5364.009
rs2341717	3	98913821	A	G	A	0.21	0	12310	0.999	-0.444	0.099	6.79E-06	4044.402
rs73676501	7	7090025	T	A	A	0.02	0	12310	0.995	-1.529	0.34	6.84E-06	365.5442
rs75361129	5	118250360	C	T	T	0.01	0	12310	0.996	-1.663	0.37	6.95E-06	316.398
rs150229484	11	70983910	CCA	C	C	0.12	0	12310	0.83	-0.631	0.14	6.99E-06	2125.299
rs148893024	11	113663454	T	A	A	0.01	0	12309	0.996	-1.781	0.396	7.03E-06	276.7127
rs2242642	14	80286306	C	G	G	0.47	0	12309	0.998	-0.361	0.08	7.22E-06	6128.027
rs115139710	5	118262011	G	A	A	0.01	0	12310	0.996	-1.660	0.37	7.25E-06	316.239
rs115837370	9	135886735	G	A	A	0.01	0	12310	0.924	-1.925	0.43	7.40E-06	229.301
rs77669066	5	50223773	A	G	G	0.02	0	12309	0.998	-1.357	0.303	7.69E-06	473.446
rs17091578	14	32388774	C	G	G	0.27	0	12310	0.979	-0.408	0.091	7.84E-06	4845.766
rs73922237	19	8206553	C	T	C	0.36	0	12310	0.993	-0.375	0.084	7.85E-06	5645.09
rs7007843	8	59111965	G	T	T	0.04	0	12309	0.999	-0.941	0.211	7.92E-06	942.655
rs77927049	14	81543731	G	A	A	0.02	0	12309	0.998	1.456	0.326	7.92E-06	404.9763
X:135890564:T:TTTTG	-	135890564	T	TTTTG	TTTTG	0.02	0	12297	0.954	1.265	0.283	7.93E-06	304.424
rs201573719	11	113668782	ATGC	A	A	0.01	0	12309	0.992	-1.767	0.396	7.97E-06	278.8606
rs56345969	17	78171236	G	A	A	0.03	0	12310	0.933	1.175	0.263	8.05E-06	590.0293
rs145115978	3	98897408	T	TAAAG	T	0.21	0	12310	0.999	-0.440	0.099	8.12E-06	4050.468
rs62346660	4	146233605	A	G	G	0.03	0	12310	0.806	-1.175	0.263	8.12E-06	587.068
rs77893100	5	50223043	C	G	G	0.02	0	12309	0.997	-1.353	0.303	8.20E-06	473.508
rs3958407	5	50236508	C	T	T	0.02	0	12309	0.935	-1.328	0.298	8.30E-06	499.257
rs11710896	3	98950647	C	A	A	0.19	0	12310	0.999	0.457	0.103	8.38E-06	3728.466
rs10501248	11	41083620	C	A	A	0.42	2	12310	1	-0.360	0.081	8.44E-06	6016.137
rs73149623	3	98938539	G	A	A	0.19	0	12310	0.997	0.457	0.103	8.56E-06	3725.718
rs10264133	7	27231097	C	T	T	0.02	0	12310	0.989	-1.277	0.287	8.71E-06	518.5753
rs4985364	16	70806674	C	T	C	0.17	0	12310	0.996	0.479	0.108	8.74E-06	3530.366
rs143528581	13	66676730	AAAT	A	A	0.02	0	12310	0.992	1.264	0.284	8.77E-06	501.6103
rs2242646	14	80288888	A	G	G	0.47	2	12309	1	-0.357	0.08	8.78E-06	6130.353
rs112149005	-	135948278	G	A	A	0.02	0	12297	0.956	1.284	0.289	9.04E-06	287.876
rs1092312	3	98908158	G	A	G	0.21	0	12310	1	-0.438	0.099	9.10E-06	4048.893
rs10768363	11	38257707	C	T	C	0.08	0	12310	0.999	0.697	0.157	9.42E-06	1889.938
rs62273517	3	111225082	G	A	A	0.07	0	12310	0.967	-0.707	0.16	9.44E-06	1535.633

rs4928154	3	98899033	C	A	C	0.21	2	12310	1	-0.436	0.099	9.62E-06	4071.562
rs774972	3	98902911	C	T	C	0.21	2	12310	1	-0.436	0.099	9.62E-06	4071.562
rs74317030	5	50221498	A	T	T	0.02	0	12309	0.997	-1.343	0.304	9.64E-06	473.664
12:102270520:T:C	12	102270520	T	C	C	0.01	0	12310	0.881	-1.665	0.376	9.67E-06	297.9433
rs1082507	3	98916453	C	T	C	0.21	0	12310	1	-0.436	0.099	9.68E-06	4044.209
12:91777215:A:AGGGAGTTGCTTGAGTTGTCAGC	12	91777215	A	AGGGAGTTGCTTGAGTTGTCAGC		0.1	0	12310	0.989	0.586	0.133	9.68E-06	2216.235
rs140015087	17	27187143	G	A	A	0.04	0	12310	0.997	0.873	0.198	9.70E-06	976.176
rs1082509	3	98916822	T	C	T	0.21	0	12310	1	-0.436	0.099	9.71E-06	4044.096
7:66562845:AT:A	7	66562845	AT	A	A	0.27	0	12310	0.877	-0.440	0.099	9.77E-06	4381.671
3:98914294:T:TACC	3	98914294	T	TACC	T	0.21	0	12310	0.999	-0.436	0.099	9.79E-06	4045.996
12:108591180:AG:A	12	108591180	AG	A	AG	0.45	0	12310	0.997	0.356	0.081	9.82E-06	6093.3
rs1066358	3	98911343	A	G	A	0.21	0	12310	0.999	-0.436	0.099	9.84E-06	4045.5
rs1066359	3	98910719	A	G	A	0.21	0	12310	0.999	-0.436	0.099	9.84E-06	4045.622
rs1066360	3	98910706	C	T	C	0.21	0	12310	0.999	-0.436	0.099	9.84E-06	4045.625
rs1066361	3	98910395	C	A	C	0.21	0	12310	0.999	-0.436	0.099	9.85E-06	4045.687
rs1082510	3	98916842	G	A	G	0.21	0	12310	1	-0.436	0.099	9.86E-06	4044.38
rs1082512	3	98917002	T	G	T	0.21	0	12310	1	-0.436	0.099	9.86E-06	4044.346
rs1066364	3	98906623	A	G	A	0.21	0	12310	1	-0.436	0.099	9.90E-06	4046.427
rs1066365	3	98906197	C	A	C	0.21	0	12310	1	-0.436	0.099	9.90E-06	4046.51
rs1066366	3	98905942	G	T	G	0.21	0	12310	1	-0.436	0.099	9.91E-06	4046.56
rs76128500	3	21197126	C	T	T	0.04	0	12310	0.999	-0.909	0.206	9.99E-06	1036.622

CHR=chromosome. In the geno. (genotyping) column, 0=imputed SNP and 2=genotyped SNP. Info refers to info score for imputation (indicating imputation quality); all imputed SNPs had info scores ≥ 0.80. AlleleA is the tested allele. MAF is the estimated minor allele frequency and is ≥ 0.01 for all SNPs. Position is given in genome build GRCh37/hg19. effN, or the "effective minor allele count" of a variant, is defined as 2p(1-p)Nv, where p is the estimated minor allele frequency, N is the sample size, and v is "oevar", a measure of imputation accuracy. If a SNP is genotyped, then oevar =1. For imputed genotypes, oevar is the ratio between the observed variance of the genotype dosage to the expected binomial variance, based on the estimated minor allele frequency p; effN is >30 for all SNPs.

Supplemental Table 3: Genome-wide association study (GWAS) results for the top loci ($p<1x10^{-5}$) with the depressive symptom score, after excluding medication users

SNP	CHR	position	alleleA	alleleB	Minor allele	MAF	geno	n	info	Beta	SE	pval	effN
12:102245668:C:T	12	102245668	C	T	T	0.01	0	11486	0.981	-2.025	0.375	6.69E-08	256.194
rs2004237	19	8209194	T	C	C	0.31	0	11486	0.995	0.445	0.083	7.54E-08	4942.087
rs62123284	19	8214984	A	G	G	0.31	2	11486	1	0.445	0.083	7.68E-08	4930.978
12:102237322:G:A	12	102237322	G	A	A	0.01	0	11486	0.977	-2.021	0.377	8.32E-08	254.176
rs3813771	19	8213590	C	T	T	0.31	0	11486	0.999	0.442	0.083	9.91E-08	4911.616
12:102238063:GA:G	12	102238063	GA	G	G	0.01	0	11486	0.98	-2.005	0.377	1.06E-07	252.937
rs77219363	20	24489072	C	CCAG GCTG ATCT	C	0.03	0	11486	0.814	1.246	0.235	1.17E-07	618.839
rs34208798	7	66518851	G	A	A	0.19	0	11486	0.999	-0.523	0.100	1.87E-07	3483.219
rs5841036	20	24502210	T	TG	T	0.02	0	11486	0.9	1.577	0.303	1.98E-07	376.544
rs11761677	7	66513614	G	A	A	0.19	0	11486	0.999	-0.516	0.100	2.45E-07	3520.986
7:66564018:AT:A	7	66564018	AT	A	A	0.21	0	11486	0.953	-0.508	0.099	3.06E-07	3655.469
rs10228308	7	66515614	T	C	C	0.19	2	11486	1	-0.512	0.100	3.13E-07	3511.967
rs10238245	7	66515394	G	A	A	0.19	0	11486	1	-0.512	0.100	3.16E-07	3512.144
rs6603149	19	8213231	A	G	G	0.38	2	11486	1	0.402	0.079	3.41E-07	5421.175
rs10234407	7	66514708	G	A	A	0.19	0	11486	1	-0.506	0.100	4.33E-07	3515.331
rs12198471	6	6906545	C	T	T	0.20	2	11486	1	0.496	0.098	4.39E-07	3620.924
rs10268701	7	66515528	C	G	G	0.19	0	11486	0.995	-0.501	0.100	4.95E-07	3562.989
rs10242790	7	66516641	A	G	A	0.19	0	11486	0.999	0.503	0.100	5.01E-07	3518.006
rs7808645	7	66514516	A	T	T	0.19	0	11486	0.991	-0.507	0.101	5.06E-07	3476.368
rs113737600	7	66615118	C	A	A	0.16	0	11486	0.993	-0.532	0.106	5.19E-07	3090.579
rs73922237	19	8206553	C	T	C	0.36	0	11486	0.993	-0.402	0.080	5.25E-07	5274.340
rs140262007	6	46983470	T	C	C	0.02	0	11486	0.983	-1.330	0.266	5.84E-07	515.618
rs35157681	19	8211519	CAG	C	C	0.39	0	11486	0.996	0.392	0.079	6.35E-07	5476.678
19:8208659:G:GC	19	8208659	G	GC	GC	0.36	0	11486	0.995	0.398	0.080	6.68E-07	5281.083
rs7252378	19	8208906	T	C	C	0.36	0	11486	0.995	0.398	0.080	6.85E-07	5285.693
rs55777322	7	66559640	T	G	G	0.19	0	11486	0.986	-0.501	0.101	7.32E-07	3467.878
rs10228812	7	66561114	C	T	T	0.20	0	11486	0.998	-0.485	0.098	7.7E-07	3639.719
19:8208664:A:ATGCAGG	19	8208664	A	ATGC AGG	ATGCAG G	0.36	0	11486	0.993	0.397	0.080	7.92E-07	5270.762
rs10611601	7	70044230	TAA	T	TAA	0.43	0	11486	0.849	-0.412	0.083	8.04E-07	4744.694
rs60558810	19	8208022	G	T	T	0.38	2	11486	1	0.385	0.078	8.51E-07	5386.932
rs2004238	19	8209192	G	A	A	0.36	0	11486	0.995	0.393	0.080	9.14E-07	5283.890

rs7252264	19	8208867	T	G	G	0.36	0	11486	0.996	0.393	0.080	9.37E-07	5282.433
rs4985364	16	70806674	C	T	C	0.17	0	11486	0.996	0.502	0.102	9.37E-07	3276.125
12:102270520:T:C	12	102270520	T	C	C	0.01	0	11486	0.881	-1.763	0.360	9.54E-07	274.032
rs11761516	7	66525513	T	C	T	0.19	0	11486	0.997	0.490	0.100	9.57E-07	3530.074
rs149113795	6	46983675	C	T	T	0.02	0	11486	0.98	-1.307	0.267	9.71E-07	513.350
19:8208662:C:G	19	8208662	C	G	G	0.36	0	11486	0.996	0.392	0.080	9.87E-07	5281.954
rs12154876	7	66563135	A	G	G	0.19	0	11486	0.999	-0.490	0.100	9.96E-07	3504.860
rs7507795	19	8208548	T	C	C	0.36	0	11486	0.995	0.392	0.080	1.00E-06	5283.381
rs373861332	7	66557326	T	G	G	0.19	0	11486	0.999	-0.489	0.100	1.02E-06	3506.328
rs143925771	7	66578612	C	T	T	0.19	0	11486	0.999	-0.489	0.100	1.03E-06	3497.805
rs58448907	7	66595583	A	G	G	0.19	0	11486	0.999	-0.489	0.100	1.06E-06	3494.273
rs7809649	7	66602947	A	G	G	0.19	0	11486	0.998	-0.489	0.100	1.1E-06	3484.479
rs2140564	7	66590824	G	C	C	0.19	0	11486	0.999	-0.488	0.100	1.14E-06	3492.417
rs7782407	7	66546243	A	G	G	0.19	0	11486	0.999	-0.485	0.100	1.19E-06	3519.207
rs7791271	7	66602986	C	T	T	0.19	0	11486	0.999	-0.486	0.100	1.19E-06	3522.731
rs72662446	8	59113186	C	T	T	0.03	2	11485	1	-1.079	0.222	1.20E-06	696.494
12:124545626:A:G	12	124545626	A	G	G	0.01	0	11486	0.8	-1.875	0.386	1.22E-06	225.442
rs7839850	8	59087582	C	A	A	0.03	2	11485	1	-1.128	0.233	1.24E-06	622.168
rs12333596	7	66551407	G	A	A	0.19	0	11486	0.999	-0.484	0.100	1.25E-06	3529.750
rs17144784	7	66551370	G	A	A	0.19	0	11486	0.999	-0.484	0.100	1.25E-06	3529.749
rs10231655	7	66552282	A	G	G	0.19	0	11486	0.999	-0.484	0.100	1.25E-06	3529.775
rs13222968	7	66533077	T	C	C	0.19	0	11486	1	-0.483	0.100	1.26E-06	3537.711
rs112483740	7	66528519	C	CAAA T	CAAAT	0.19	0	11486	0.999	-0.483	0.100	1.27E-06	3538.905
rs28857233	7	66528050	T	A	A	0.19	0	11486	0.984	-0.484	0.100	1.27E-06	3579.536
rs10226634	7	66550307	T	C	C	0.19	0	11486	0.999	-0.484	0.100	1.27E-06	3529.865
rs28484969	7	66555347	G	T	T	0.19	0	11486	0.999	-0.484	0.100	1.27E-06	3529.894
rs34813948	7	66529741	C	G	G	0.19	0	11486	1	-0.483	0.100	1.27E-06	3537.693
rs10273674	7	66517049	C	T	T	0.19	0	11486	0.999	-0.484	0.100	1.29E-06	3527.136
rs71563157	7	66555846	G	A	A	0.19	0	11486	1	-0.483	0.100	1.3E-06	3530.144
rs66859603	7	66557148	C	T	T	0.19	0	11486	0.999	-0.483	0.100	1.3E-06	3530.167
rs2711913	7	66557020	C	G	G	0.19	0	11486	0.999	-0.483	0.100	1.3E-06	3530.164
rs55994185	7	66557950	G	A	A	0.19	0	11486	0.999	-0.483	0.100	1.3E-06	3530.182
rs55974240	7	66558071	C	T	T	0.19	0	11486	0.999	-0.483	0.100	1.3E-06	3530.185
rs7194091	16	70786780	C	T	C	0.19	0	11486	0.989	0.493	0.102	1.30E-06	3472.249
rs10228932	7	66561217	C	A	A	0.19	0	11486	0.999	-0.483	0.100	1.31E-06	3530.263
rs10269571	7	66516151	C	T	T	0.19	0	11486	1	-0.483	0.100	1.33E-06	3527.077
rs35956465	19	8211754	AG	A	A	0.39	0	11486	0.997	0.379	0.079	1.40E-06	5487.468

rs6957569	7	66562441	G	A	A	0.19	0	11486	0.999	-0.482	0.100	1.4E-06	3531.346
rs67737819	7	66566448	G	A	A	0.19	0	11486	0.999	-0.482	0.100	1.41E-06	3518.352
rs2049831	14	80289134	G	A	A	0.46	0	11485	0.998	-0.368	0.076	1.44E-06	5709.407
rs11524606	7	66522546	C	T	T	0.19	0	11486	0.999	-0.480	0.100	1.47E-06	3537.435
rs7252385	19	8208921	C	T	C	0.36	0	11486	0.995	-0.386	0.080	1.47E-06	5282.160
rs35913158	7	66584841	C	T	T	0.19	0	11486	0.999	-0.482	0.100	1.47E-06	3507.864
rs12698557	7	66521471	T	C	C	0.19	0	11486	0.999	-0.480	0.100	1.52E-06	3537.374
rs59540627	7	66528654	G	C	C	0.19	0	11486	0.999	-0.480	0.100	1.53E-06	3540.464
rs7807231	7	66543514	T	A	A	0.19	0	11486	1	-0.479	0.100	1.56E-06	3539.987
rs10252479	7	66541889	C	A	A	0.19	0	11486	1	-0.479	0.100	1.56E-06	3539.988
rs10281398	7	66542135	G	A	A	0.19	0	11486	1	-0.479	0.100	1.56E-06	3539.988
rs10280810	7	66541706	G	A	A	0.19	0	11486	1	-0.479	0.100	1.56E-06	3539.988
rs7794380	7	66545725	G	C	C	0.19	0	11486	1	-0.479	0.100	1.56E-06	3539.986
rs12334126	7	66539772	G	A	A	0.19	0	11486	1	-0.479	0.100	1.56E-06	3539.990
rs2711923	7	66546656	G	C	C	0.19	0	11486	1	-0.479	0.100	1.57E-06	3540.068
rs58942690	7	66538918	C	A	A	0.19	0	11486	0.997	-0.479	0.100	1.57E-06	3550.784
rs11771640	7	66547296	T	G	G	0.19	0	11486	1	-0.479	0.100	1.57E-06	3540.151
rs11348807	7	66549247	TA	T	T	0.19	0	11486	1	-0.479	0.100	1.57E-06	3540.223
rs67178340	7	66538797	C	T	T	0.19	0	11486	0.999	-0.479	0.100	1.58E-06	3540.523
rs71563154	7	66538714	T	C	C	0.19	0	11486	0.999	-0.479	0.100	1.59E-06	3540.576
rs71563153	7	66538688	G	T	T	0.19	0	11486	0.999	-0.479	0.100	1.59E-06	3540.591
rs55731089	7	66520438	C	T	T	0.19	0	11486	0.999	-0.479	0.100	1.59E-06	3537.335
rs74024449	16	70786167	C	T	T	0.18	0	11486	0.983	-0.491	0.102	1.59E-06	3448.269
rs2242643	14	80286394	T	C	C	0.46	0	11485	0.998	-0.367	0.076	1.61E-06	5705.960
rs2242648	14	80297210	G	C	C	0.46	0	11485	0.999	-0.367	0.076	1.62E-06	5707.584
rs186222942	20	24548719	G	A	A	0.01	0	11486	0.951	-1.773	0.370	1.63E-06	252.476
rs11314136	7	66519689	AT	A	A	0.19	0	11486	0.999	-0.478	0.100	1.64E-06	3537.244
rs78316461	7	66513067	G	A	A	0.19	0	11486	0.999	-0.478	0.100	1.66E-06	3537.226
rs34157075	7	66512317	A	C	C	0.19	0	11486	0.999	-0.478	0.100	1.66E-06	3537.322
rs10249716	7	66523521	G	T	T	0.19	0	11486	0.998	-0.478	0.100	1.68E-06	3539.525
rs4756630	11	41066100	C	T	T	0.38	2	11486	1	-0.380	0.079	1.68E-06	5429.874
rs10259711	7	66518946	C	T	T	0.19	0	11486	0.999	-0.478	0.100	1.69E-06	3537.192
rs34840198	1	156128822	CA	C	C	0.47	0	11486	0.825	-0.400	0.084	1.69E-06	4766.946
rs78047560	8	59119854	TG	TGG	TGG	0.08	0	11485	0.958	-0.680	0.142	1.72E-06	1723.124
rs6973836	7	66569208	G	A	A	0.19	0	11486	0.999	-0.478	0.100	1.72E-06	3520.239
rs7783157	7	66574420	A	C	C	0.19	0	11486	0.998	-0.478	0.100	1.73E-06	3518.229
rs7800350	7	66567698	G	T	T	0.19	0	11486	0.999	-0.476	0.100	1.78E-06	3542.170

rs10501248	11	41083620	C	A	A	0.43	2	11486	1	-0.367	0.077	1.80E-06	5616.156
rs28888140	7	66593134	T	C	C	0.19	0	11486	1	-0.476	0.100	1.84E-06	3531.343
rs58756282	7	66584920	C	T	T	0.19	0	11486	1	-0.476	0.100	1.85E-06	3531.574
rs10224763	7	66586221	A	G	G	0.19	0	11486	1	-0.476	0.100	1.85E-06	3531.572
rs10274580	7	66592378	C	A	A	0.19	0	11486	1	-0.476	0.100	1.85E-06	3531.291
rs60910884	7	66598251	C	T	T	0.19	0	11486	1	-0.476	0.100	1.85E-06	3531.285
rs10233183	7	66597207	C	T	T	0.19	0	11486	1	-0.476	0.100	1.85E-06	3531.285
rs149883819	7	66600352	C	CA	CA	0.19	0	11486	1	-0.476	0.100	1.85E-06	3531.237
rs17144710	7	66584459	G	T	G	0.19	0	11486	0.999	0.476	0.100	1.89E-06	3530.302
rs6975866	7	66543980	C	T	C	0.19	0	11486	0.999	0.475	0.100	1.89E-06	3538.555
rs55704136	7	66589409	G	C	C	0.19	0	11486	0.999	-0.475	0.100	1.89E-06	3542.977
rs10249587	7	66523392	G	A	A	0.19	0	11486	0.999	-0.475	0.100	1.9E-06	3540.562
rs13243892	7	66576213	C	T	T	0.19	0	11486	0.999	-0.476	0.100	1.91E-06	3521.140
rs59201833	19	8207844	G	A	A	0.33	0	11486	0.977	0.393	0.083	1.94E-06	5048.084
rs916894	17	36084261	A	G	G	0.10	0	11486	0.923	-0.630	0.133	1.98E-06	2017.712
rs80291665	8	40389404	G	A	A	0.03	2	11485	1	1.027	0.216	2.01E-06	747.919
rs62123277	19	8207872	G	T	T	0.33	0	11486	0.976	0.392	0.083	2.04E-06	5046.153
rs75776756	19	8207876	C	T	T	0.33	0	11486	0.976	0.392	0.083	2.04E-06	5046.143
rs78539876	19	8207877	C	G	G	0.33	0	11486	0.976	0.392	0.083	2.04E-06	5046.142
rs28482454	3	171798234	T	A	A	0.35	0	11486	0.699	-0.452	0.095	2.05E-06	3666.545
rs71535636	7	66512581	T	C	C	0.19	0	11486	0.999	-0.473	0.100	2.11E-06	3534.267
rs2960970	7	66574209	C	T	T	0.19	0	11486	1	-0.472	0.100	2.17E-06	3544.003
rs7645414	3	99173312	C	T	T	0.06	0	11486	1	-0.759	0.160	2.17E-06	1332.223
rs59247139	7	66574425	C	T	T	0.19	0	11486	0.999	-0.472	0.100	2.17E-06	3541.983
rs2902122	11	41098011	T	C	C	0.42	0	11486	0.997	-0.365	0.077	2.20E-06	5594.541
rs17248914	16	70785197	G	A	C	0.11	0	11486	0.985	0.572	0.121	2.26E-06	2315.846
rs72052718	17	36084292	CTGGTTCTCAAATTTAGCTACACAT	C	C	0.10	0	11486	0.917	-0.627	0.133	2.33E-06	2008.498
rs115925701	4	144540332	A	G	A	0.01	0	11486	0.875	-1.696	0.361	2.66E-06	257.719
rs2154265	10	56305290	T	C	C	0.42	0	11486	0.988	0.368	0.079	2.79E-06	5582.634
rs2242646	14	80288888	A	G	G	0.47	2	11485	1	-0.357	0.076	2.99E-06	5717.881
rs35562863	15	88174604	T	C	C	0.02	0	11486	0.999	-1.467	0.314	3.05E-06	355.363
rs59852863	7	66546207	CTTTT	C	C	0.20	0	11486	0.993	-0.462	0.099	3.12E-06	3607.390
rs7793589	7	66608855	G	T	T	0.18	0	11486	0.997	-0.475	0.102	3.4E-06	3330.362
rs200584538	7	66717880	C	CAAA T	CAAAT	0.10	0	11486	0.95	-0.588	0.127	3.62E-06	2057.495
rs2977371	8	59141390	G	A	A	0.07	0	11485	1	-0.715	0.154	3.66E-06	1438.482
rs148833388	18	57166108	C	T	T	0.01	0	11485	0.99	-1.531	0.331	3.74E-06	323.318

rs8022130	14	96542273	T	C	C	0.29	2	11485	1	-0.391	0.084	3.79E-06	4683.956
rs2242645	14	80288484	G	A	A	0.47	2	11485	1	-0.353	0.076	3.86E-06	5717.684
rs62123280	19	8214703	C	T	T	0.41	0	11486	0.998	0.361	0.078	3.93E-06	5551.803
rs62123281	19	8214705	A	G	G	0.41	0	11486	0.998	0.361	0.078	3.93E-06	5551.807
rs35415540	19	8215589	C	A	A	0.37	2	11486	1	0.365	0.079	4.06E-06	5355.906
rs12929374	16	70827361	T	C	C	0.13	0	11486	0.994	-0.520	0.113	4.13E-06	2640.807
rs10984901	9	123156657	T	G	G	0.41	0	11486	0.963	-0.375	0.082	4.16E-06	5553.901
rs2242642	14	80286306	C	G	G	0.47	0	11485	0.998	-0.352	0.077	4.21E-06	5715.324
7:66562845:AT:A	7	66562845	AT	A	A	0.27	0	11486	0.877	-0.435	0.095	4.35E-06	4065.226
rs9932965	16	70783213	T	G	G	0.18	0	11486	0.887	-0.494	0.108	4.43E-06	3151.504
rs139161230	8	40357315	A	G	G	0.04	0	11485	0.999	0.933	0.203	4.44E-06	850.767
rs6974864	7	66506086	G	A	A	0.20	2	11486	1	-0.453	0.099	4.46E-06	3623.963
rs10271374	7	66506237	T	A	A	0.20	0	11486	1	-0.453	0.099	4.48E-06	3623.954
12:65422472:AT:A	12	65422472	AT	A	A	0.04	0	11486	0.94	-0.935	0.204	4.48E-06	827.666
rs200905081	7	66610751	G	GT	GT	0.18	0	11486	0.998	-0.468	0.102	4.52E-06	3335.133
rs75307325	18	57164517	A	G	G	0.01	0	11485	0.99	-1.519	0.331	4.58E-06	322.521
rs55719516	8	59114301	T	C	C	0.03	0	11485	0.999	-0.979	0.214	4.60E-06	763.499
rs10825348	10	56303614	T	A	A	0.41	0	11486	0.993	0.360	0.079	4.64E-06	5559.018
rs76602712	15	58798307	G	A	A	0.10	2	11486	1	-0.590	0.129	4.64E-06	2034.446
rs7007843	8	59111965	G	T	T	0.04	0	11485	0.999	-0.922	0.201	4.74E-06	861.798
rs59397156	11	96869427	GAA	G	G	0.04	0	11485	0.858	0.993	0.217	4.87E-06	758.970
rs111563222	8	40368370	C	T	T	0.04	0	11485	0.998	0.929	0.203	4.92E-06	852.421
rs2970750	8	59138556	T	G	G	0.07	2	11485	1	-0.704	0.154	4.93E-06	1441.946
rs35122750	7	66607147	A	G	G	0.18	0	11486	0.999	-0.466	0.102	4.98E-06	3355.644
12:65434552:G:A	12	65434552	G	A	A	0.04	0	11486	0.942	-0.931	0.204	5.03E-06	827.046
rs4859144	3	182624759	C	T	T	0.44	0	11486	1	0.346	0.076	5.06E-06	5671.314
rs113125929	8	40354592	G	A	A	0.04	0	11485	0.998	0.930	0.204	5.12E-06	847.970
rs71401831	16	70815545	G	A	A	0.13	0	11486	0.997	-0.515	0.113	5.13E-06	2632.280
rs7793104	7	66621061	C	T	T	0.18	0	11486	0.999	-0.465	0.102	5.16E-06	3341.901
rs11260062	19	8214970	A	C	C	0.42	2	11486	1	0.353	0.077	5.16E-06	5611.508
rs7776751	7	66608570	A	G	G	0.18	0	11486	0.999	-0.465	0.102	5.19E-06	3341.949
rs675071	3	182604826	T	C	T	0.44	2	11486	1	-0.346	0.076	5.22E-06	5671.678
rs139625516	8	59132395	TG	T	T	0.07	0	11485	0.995	-0.691	0.152	5.26E-06	1500.511
rs28465142	7	66611347	A	C	C	0.18	0	11486	0.999	-0.464	0.102	5.31E-06	3359.333
rs11004372	10	56304691	A	G	G	0.41	0	11486	0.995	0.357	0.079	5.40E-06	5568.660
rs8127353	21	44076975	G	T	T	0.02	2	11485	1	-1.272	0.280	5.44E-06	436.379
rs75592841	5	123596119	A	G	G	0.05	0	11486	0.975	-0.789	0.174	5.55E-06	1079.882

rs7188712	16	70795402	C	T	T	0.14	0	11486	0.998	-0.507	0.112	5.55E-06	2792.487
rs28795765	8	59126506	C	T	T	0.07	2	11485	1	-0.683	0.150	5.56E-06	1519.479
rs2970748	8	59130869	G	A	A	0.07	0	11485	0.996	-0.685	0.151	5.64E-06	1512.288
rs686476	3	182587666	T	C	T	0.44	0	11486	1	-0.345	0.076	5.73E-06	5658.997
rs113787472	8	59128896	G	A	A	0.07	0	11485	0.997	-0.684	0.151	5.76E-06	1515.899
rs77511802	5	123590468	A	G	G	0.06	0	11486	0.991	-0.737	0.163	5.93E-06	1226.850
rs11724589	4	145893275	G	A	G	0.13	0	11486	0.992	0.521	0.115	5.95E-06	2624.716
rs72662466	8	59126940	G	A	A	0.07	0	11485	0.999	-0.681	0.150	5.96E-06	1519.475
rs7113187	11	41098007	A	C	A	0.46	0	11486	0.998	0.346	0.076	5.98E-06	5698.880
rs150878459	16	70763729	T	TTGAA	TTGAA	0.13	0	11486	0.972	-0.524	0.116	6.01E-06	2543.983
rs77078152	18	57179763	G	A	A	0.01	0	11485	0.99	-1.760	0.389	6.03E-06	234.199
rs7099825	10	56304265	A	G	G	0.41	2	11486	1	0.354	0.078	6.09E-06	5570.265
rs2900169	9	123185724	T	C	C	0.39	2	11486	1	-0.359	0.080	6.22E-06	5476.990
rs60929238	8	40361351	C	T	C	0.04	0	11485	0.998	-0.918	0.203	6.28E-06	852.740
rs7129748	11	41098364	T	A	T	0.46	0	11486	0.999	0.345	0.076	6.31E-06	5698.647
rs12976688	19	8205952	G	A	A	0.35	0	11486	0.975	0.368	0.081	6.32E-06	5106.259
rs3857691	7	66608420	C	G	G	0.18	0	11486	1	-0.459	0.102	6.33E-06	3383.043
rs71163568	4	11895023	T	TTAGATATAA	TTAGATAA	0.41	0	11486	0.999	0.351	0.078	6.39E-06	5477.415
rs70973707	5	90061246	C	CCA	CCA	0.18	0	11486	0.913	0.480	0.106	6.46E-06	3180.785
3:99171247:A:G	3	99171247	A	G	G	0.06	0	11486	0.977	-0.740	0.164	6.50E-06	1284.729
rs74755086	7	66556235	A	G	G	0.16	0	11486	0.919	-0.499	0.111	6.6E-06	2912.473
rs78961605	7	66556236	T	C	C	0.16	0	11486	0.919	-0.499	0.111	6.6E-06	2912.473
rs7657168	4	175485146	G	A	G	0.45	2	11486	1	-0.348	0.077	6.60E-06	5674.982
rs147890196	11	9249517	G	A	A	0.04	0	11486	0.992	-0.897	0.199	6.61E-06	800.398
rs11264449	1	156135241	G	C	C	0.34	2	11486	1	-0.365	0.081	6.65E-06	5120.679
rs369449582	3	99171252	A	G	G	0.06	0	11486	0.977	-0.739	0.164	6.68E-06	1285.022
rs4985425	16	70806867	A	C	C	0.13	0	11486	0.996	-0.508	0.113	6.68E-06	2641.678
rs10262781	7	66620160	C	T	T	0.18	0	11486	1	-0.457	0.102	6.84E-06	3380.771
rs6978918	7	66614462	T	C	C	0.18	2	11486	1	-0.457	0.102	6.84E-06	3383.648
rs7350002	7	66620603	G	A	A	0.18	0	11486	1	-0.457	0.102	6.84E-06	3380.771
rs7792212	7	66621143	G	A	A	0.18	0	11486	1	-0.457	0.102	6.85E-06	3380.770
rs9690120	7	66618358	G	A	A	0.18	0	11486	0.999	-0.457	0.102	6.93E-06	3381.236
rs12647376:	4	11891651	G	A	A	0.40	0	11486	0.999	0.350	0.078	6.96E-06	5458.731
rs3980757	7	66590764	G	A	A	0.19	0	11486	0.995	-0.447	0.100	7.12E-06	3572.676
rs111911581	5	123579970	A	G	G	0.06	0	11486	0.993	-0.725	0.162	7.12E-06	1239.048
rs150229484	11	70983910	CCA	C	C	0.11	0	11486	0.83	-0.600	0.134	7.13E-06	1971.281
rs6567089	18	57161832	G	A	A	0.01	0	11485	0.991	-1.489	0.332	7.20E-06	321.466

19:8214651:C:CGGG CGGGGGGCTCA	19	8214651	C	CGGG CGGG GGGC TCA	CGGGCG GGGGGC TCA	0.42	0	11486	0.997	0.351	0.078	7.21E-06	5578.845
rs13189820	5	171929115	C	G	G	0.49	0	11486	0.989	0.344	0.077	7.22E-06	5696.409
rs11935422	4	11894163	C	T	T	0.41	0	11486	0.998	0.349	0.078	7.32E-06	5463.564
rs58783707	14	94339237	G	A	A	0.14	2	11485	1	0.502	0.112	7.34E-06	2735.416
rs2049285	3	182591147	T	G	T	0.45	0	11486	1	-0.340	0.076	7.37E-06	5683.479
7:66556243:T:C	7	66556243	T	C	C	0.16	0	11486	0.912	-0.499	0.111	7.51E-06	2866.861
7:66556244:T:C	7	66556244	T	C	C	0.16	0	11486	0.912	-0.499	0.111	7.51E-06	2866.861
7:66556248:T:G	7	66556248	T	G	G	0.16	0	11486	0.912	-0.499	0.111	7.51E-06	2866.862
rs2866059	4	11892822	C	T	T	0.40	2	11486	1	0.348	0.078	7.75E-06	5516.509
rs73676501	7	7090025	T	A	A	0.01	0	11486	0.995	-1.451	0.325	7.91E-06	333.159
rs2687052	7	66621824	A	G	G	0.18	0	11486	0.998	-0.455	0.102	7.99E-06	3361.275
rs10244331	7	66622569	G	A	A	0.18	0	11486	0.999	-0.454	0.102	8.06E-06	3380.754
rs6567088	18	57157852	C	T	T	0.01	0	11485	0.997	-1.502	0.337	8.09E-06	310.949
rs74774740	10	106247951	A	G	A	0.06	0	11486	0.909	0.738	0.165	8.10E-06	1278.943
rs1876380	8	59123769	C	T	T	0.07	0	11485	1	-0.697	0.156	8.17E-06	1403.395
rs13144693	4	169528576	A	G	G	0.41	0	11486	0.992	0.351	0.079	8.19E-06	5466.476
rs10009735	4	11871016	C	T	T	0.46	0	11486	0.998	0.345	0.077	8.19E-06	5651.094
rs72662423	8	59080053	C	T	T	0.02	0	11485	0.983	-1.250	0.280	8.29E-06	428.940
rs28676580	16	70806324	T	G	G	0.19	0	11486	0.996	-0.443	0.099	8.38E-06	3515.696
rs3760118	16	70799409	T	A	A	0.12	0	11486	0.996	-0.521	0.117	8.41E-06	2450.512
rs183745482	11	113142397	C	T	T	0.15	0	11485	0.868	-0.523	0.117	8.44E-06	2759.715
rs191197325	11	113142396	G	C	C	0.15	0	11485	0.868	-0.523	0.117	8.45E-06	2759.717
rs6471687	8	59104101	G	A	A	0.04	2	11485	1	-0.883	0.198	8.55E-06	894.184
rs141823017	5	57664835	C	A	A	0.01	0	11485	0.971	-1.711	0.385	8.64E-06	226.958
rs71126901	3	73807404	G	GAAC	GAAC	0.43	0	11486	0.937	0.359	0.081	8.67E-06	5521.591
rs75939523	8	40375092	T	C	T	0.04	0	11485	0.986	-0.901	0.203	8.68E-06	865.482
rs35513823	4	11892172	G	GT	GT	0.40	0	11486	0.999	0.346	0.078	8.71E-06	5461.482
rs79796659	5	123595143	A	G	G	0.06	0	11486	0.985	-0.727	0.163	8.73E-06	1218.398
rs7698006	4	11884791	T	A	A	0.39	0	11486	0.99	0.350	0.079	8.74E-06	5343.947
rs11852442	15	88175304	G	A	A	0.02	2	11486	1	-1.372	0.309	8.76E-06	367.911
rs10742575	11	41112780	A	C	C	0.39	0	11486	0.998	-0.348	0.078	9.00E-06	5474.881
rs34492261	3	182616938	ATT	A	A	0.43	0	11486	0.986	0.340	0.077	9.07E-06	5645.655
rs79912088	18	57151036	A	G	G	0.01	0	11485	0.999	-1.480	0.334	9.08E-06	314.894
rs6843251	4	11873630	A	G	G	0.46	2	11486	1	0.343	0.077	9.17E-06	5709.824
rs75982171	18	57152493	A	T	T	0.01	0	11485	0.998	-1.480	0.334	9.18E-06	314.704

rs4755568	11	41106215	A	G	G	0.42	0	11486	0.999	-0.341	0.077	9.20E-06	5597.567
rs9829325	3	99171185	A	G	G	0.06	0	11486	0.996	-0.710	0.160	9.21E-06	1333.811
rs35426120	16	70833395	C	T	T	0.14	2	11486	1	-0.495	0.112	9.39E-06	2685.314
rs8093351	18	57153206	T	G	G	0.01	0	11485	0.998	-1.479	0.334	9.48E-06	314.257
rs143709214	3	99172537	G	C	C	0.06	0	11486	1	-0.718	0.162	9.49E-06	1289.177
rs2670334	3	99176840	G	A	A	0.06	2	11486	1	-0.718	0.162	9.49E-06	1289.177
rs2700660	3	99176672	G	T	T	0.06	0	11486	1	-0.718	0.162	9.49E-06	1289.177
rs35484765	3	99169636	CA	C	C	0.06	0	11486	1	-0.718	0.162	9.49E-06	1289.177
rs9846837	3	99171375	G	T	T	0.06	0	11486	1	-0.718	0.162	9.49E-06	1289.177
rs17091578	14	32388774	C	G	G	0.27	0	11486	0.979	-0.386	0.087	9.50E-06	4528.439
rs9982754	21	21043988	C	A	A	0.01	0	11485	0.899	-1.542	0.348	9.54E-06	292.844
rs2082927	4	177910886	T	G	G	0.28	0	11486	0.996	0.376	0.085	9.60E-06	4659.296
12:102286046:C:G	12	102286046	C	G	G	0.01	0	11486	0.991	-1.705	0.385	9.74E-06	238.993
rs3785417	16	70793017	G	A	G	0.28	0	11486	0.996	0.392	0.089	9.99E-06	4603.548

CHR=chromosome. In the geno. (genotyping) column, 0=imputed SNP and 2=genotyped SNP. Info refers to info score for imputation (indicating imputation quality); all imputed SNPs had info scores ≥ 0.80. AlleleA is the tested allele. MAF is the estimated minor allele frequency and is ≥ 0.01 for all SNPs. Position is given in genome build GRCh37/hg19. effN, or the "effective minor allele count" of a variant, is defined as 2p(1-p)Nv, where p is the estimated minor allele frequency, N is the sample size, and v is "oevar", a measure of imputation accuracy. If a SNP is genotyped, then oevar =1. For imputed genotypes, oevar is the ratio between the observed variance of the genotype dosage to the expected binomial variance, based on the estimated minor allele frequency p; effN is >30 for all SNPs.

Supplemental Table 4: Genome-wide association study (GWAS) results for the top loci ($p<1x10^{-6}$) with the original depressive symptom score

SNP	CHR	position	alleleA	alleleB	Minor allele	MAF	geno	n	info	Beta	SE	pval	effN
12:102245668:C:T	12	102245668	C	T	T	0.01	0	12310	0.981	-2.024	0.390	2.07E-07	282.793
12:102237322:G:A	12	102237322	G	A	A	0.01	0	12310	0.977	-2.029	0.392	2.23E-07	280.804
12:102238063:GA:G	12	102238063	GA	G	G	0.01	0	12310	0.98	-2.017	0.392	2.65E-07	279.528
rs56712382	5	39209149	G	GCA	GCA	0.28	0	12310	0.893	0.487	0.099	9.75E-07	4761.030
rs9599044	13	66494976	T	A	T	0.03	0	12310	0.961	1.242	0.254	1.00E-06	631.326
rs5841036	20	24502210	T	TG	T	0.02	0	12310	0.9	1.546	0.317	1.04E-06	408.146
7:66564018:AT:A	7	66564018	AT	A	A	0.21	0	12310	0.953	-0.508	0.104	1.11E-06	3952.047
rs10268701	7	66515528	C	G	G	0.19	0	12310	0.995	-0.509	0.105	1.12E-06	3856.418
rs7198462	16	77395589	T	C	C	0.01	0	12310	0.972	-2.036	0.419	1.15E-06	243.704
rs11761677	7	66513614	G	A	A	0.19	0	12310	0.999	-0.510	0.105	1.16E-06	3808.594
rs10228308	7	66515614	T	C	C	0.19	2	12310	1	-0.509	0.105	1.24E-06	3799.051
rs10238245	7	66515394	G	A	A	0.19	0	12310	1	-0.509	0.105	1.26E-06	3799.227
rs12198471	6	6906545	C	T	T	0.20	2	12310	1	0.498	0.103	1.29E-06	3899.423
rs138895464	11	113660083	A	T	T	0.01	0	12309	0.995	-1.764	0.365	1.31E-06	327.441
rs10234407	7	66514708	G	A	A	0.19	0	12310	1	-0.506	0.105	1.44E-06	3803.627
rs34208798	7	66518851	G	A	A	0.19	0	12310	0.999	-0.507	0.105	1.47E-06	3764.943
rs55777322	7	66559640	T	G	G	0.19	0	12310	0.986	-0.511	0.106	1.48E-06	3754.231
rs10242790	7	66516641	A	G	A	0.19	0	12310	0.999	0.504	0.105	1.61E-06	3806.535
rs117254441	16	52657128	T	C	T	0.03	0	12310	0.842	1.128	0.236	1.76E-06	720.492
rs7808645	7	66514516	A	T	T	0.19	0	12310	0.991	-0.503	0.106	2.06E-06	3760.580
rs2242643	14	80286394	T	C	C	0.46	0	12309	0.998	-0.380	0.080	2.18E-06	6118.670
rs113737600	7	66615118	C	A	A	0.16	0	12310	0.993	-0.526	0.111	2.21E-06	3342.016
rs1462245	11	38285992	A	C	A	0.09	2	12310	1	0.729	0.154	2.35E-06	1981.208
rs373861332	7	66557326	T	G	G	0.19	0	12310	0.999	-0.496	0.105	2.35E-06	3794.917
rs12333596	7	66551407	G	A	A	0.19	0	12310	0.999	-0.493	0.105	2.48E-06	3820.430
rs17144784	7	66551370	G	A	A	0.19	0	12310	0.999	-0.493	0.105	2.48E-06	3820.429
rs10231655	7	66552282	A	G	G	0.19	0	12310	0.999	-0.493	0.105	2.48E-06	3820.455
rs28484969	7	66555347	G	T	T	0.19	0	12310	0.999	-0.493	0.105	2.51E-06	3820.571
rs10226634	7	66550307	T	C	C	0.19	0	12310	0.999	-0.493	0.105	2.52E-06	3820.544
rs71563157	7	66555846	G	A	A	0.19	0	12310	1	-0.492	0.105	2.56E-06	3820.824
rs2711913	7	66557020	C	G	G	0.19	0	12310	0.999	-0.492	0.105	2.56E-06	3820.843
rs66859603	7	66557148	C	T	T	0.19	0	12310	0.999	-0.492	0.105	2.56E-06	3820.846
rs55994185	7	66557950	G	A	A	0.19	0	12310	0.999	-0.492	0.105	2.57E-06	3820.861

rs55974240	7	66558071	C	T	T	0.19	0	12310	0.999	-0.492	0.105	2.57E-06	3820.864
rs10228932	7	66561217	C	A	A	0.19	0	12310	0.999	-0.492	0.105	2.59E-06	3820.941
rs7787409	7	85056967	T	C	T	0.04	0	12310	0.964	1.017	0.216	2.63E-06	872.479
rs11761516	7	66525513	T	C	T	0.19	0	12310	0.997	0.492	0.105	2.65E-06	3819.067
rs7782407	7	66546243	A	G	G	0.19	0	12310	0.999	-0.491	0.105	2.74E-06	3808.320
rs6957569	7	66562441	G	A	A	0.19	0	12310	0.999	-0.490	0.105	2.81E-06	3822.016
rs62123284	19	8214984	A	G	G	0.31	2	12310	1	0.407	0.087	2.83E-06	5268.421
rs13222968	7	66533077	T	C	C	0.19	0	12310	1	-0.490	0.105	2.84E-06	3827.687
rs7791271	7	66602986	C	T	T	0.19	0	12310	0.999	-0.491	0.105	2.84E-06	3810.871
rs34813948	7	66529741	C	G	G	0.19	0	12310	1	-0.489	0.105	2.87E-06	3827.670
rs10228812	7	66561114	C	T	T	0.20	0	12310	0.998	-0.482	0.103	2.87E-06	3934.739
rs112483740	7	66528519	C	CAAAT	CAAAT	0.19	0	12310	0.999	-0.489	0.105	2.89E-06	3828.914
rs55719516	8	59114301	T	C	C	0.04	0	12309	0.999	-1.042	0.223	2.89E-06	839.014
rs7807231	7	66543514	T	A	A	0.19	0	12310	1	-0.489	0.105	2.96E-06	3831.201
rs10252479	7	66541889	C	A	A	0.19	0	12310	1	-0.489	0.105	2.96E-06	3831.202
rs10281398	7	66542135	G	A	A	0.19	0	12310	1	-0.489	0.105	2.96E-06	3831.202
rs7794380	7	66545725	G	C	C	0.19	0	12310	1	-0.489	0.105	2.96E-06	3831.200
rs10280810	7	66541706	G	A	A	0.19	0	12310	1	-0.489	0.105	2.96E-06	3831.202
rs12334126	7	66539772	G	A	A	0.19	0	12310	1	-0.489	0.105	2.96E-06	3831.203
rs2711923	7	66546656	G	C	C	0.19	0	12310	1	-0.489	0.105	2.97E-06	3831.282
rs5791224	11	38286939	G	GA	G	0.09	0	12310	1	0.722	0.155	2.97E-06	1980.174
rs11771640	7	66547296	T	G	G	0.19	0	12310	1	-0.489	0.105	2.97E-06	3831.364
rs11348807	7	66549247	TA	T	T	0.19	0	12310	1	-0.488	0.105	2.98E-06	3831.435
rs59852863	7	66546207	CTTTT	C	C	0.20	0	12310	0.993	-0.485	0.104	3E-06	3905.257
rs67178340	7	66538797	C	T	T	0.19	0	12310	0.999	-0.488	0.105	3.02E-06	3831.728
rs71563154	7	66538714	T	C	C	0.19	0	12310	0.999	-0.488	0.105	3.03E-06	3831.780
rs71563153	7	66538688	G	T	T	0.19	0	12310	0.999	-0.488	0.105	3.03E-06	3831.796
rs56738524	8	8420053	A	G	A	0.34	0	12309	0.995	-0.398	0.085	3.04E-06	5512.177
rs10273674	7	66517049	C	T	T	0.19	0	12310	0.999	-0.489	0.105	3.04E-06	3816.574
rs147890196	11	9249517	G	A	A	0.04	0	12310	0.992	-0.974	0.209	3.04E-06	864.907
rs3813771	19	8213590	C	T	T	0.31	0	12310	0.999	0.407	0.087	3.05E-06	5246.758
rs10611601	7	70044230	TAA	T	TAA	0.43	0	12310	0.849	-0.411	0.088	3.06E-06	5082.999
rs1585555	11	38287507	C	T	C	0.09	0	12310	1	0.722	0.155	3.07E-06	1978.353
rs59540627	7	66528654	G	C	C	0.19	0	12310	0.999	-0.488	0.105	3.08E-06	3831.159
rs1599564	11	38288114	C	A	C	0.09	0	12310	0.999	0.721	0.155	3.09E-06	1979.385
rs2292143	5	168213007	G	A	A	0.16	2	12310	1	-0.512	0.110	3.12E-06	3339.987
rs67737819	7	66566448	G	A	A	0.19	0	12310	0.999	-0.489	0.105	3.14E-06	3807.467

rs10269571	7	66516151	C	T	T	0.19	0	12310	1	-0.488	0.105	3.15E-06	3816.516
rs55704136	7	66589409	G	C	C	0.19	0	12310	0.999	-0.487	0.104	3.18E-06	3834.800
rs10249716	7	66523521	G	T	T	0.19	0	12310	0.998	-0.487	0.105	3.26E-06	3830.591
rs11524606	7	66522546	C	T	T	0.19	0	12310	0.999	-0.487	0.105	3.28E-06	3827.413
rs35913158	7	66584841	C	T	T	0.19	0	12310	0.999	-0.488	0.105	3.32E-06	3796.464
rs28857233	7	66528050	T	A	A	0.20	0	12310	0.984	-0.487	0.105	3.36E-06	3870.664
rs17144710	7	66584459	G	T	G	0.19	0	12310	0.999	0.486	0.105	3.4E-06	3821.136
rs58942690	7	66538918	C	A	A	0.19	0	12310	0.997	-0.486	0.105	3.4E-06	3841.920
rs12698557	7	66521471	T	C	C	0.19	0	12310	0.999	-0.486	0.105	3.4E-06	3827.352
rs10825348	10	56303614	T	A	A	0.41	0	12310	0.993	0.384	0.083	3.42E-06	5946.532
rs7800350	7	66567698	G	T	T	0.19	0	12310	0.999	-0.485	0.105	3.43E-06	3833.370
rs151216651	1	237250656	T	TCTC	TCTC	0.01	0	12310	0.996	-1.741	0.375	3.48E-06	294.181
rs5975809	-	135940359	G	A	A	0.01	0	12297	0.947	1.369	0.295	3.52E-06	276.285
rs6975866	7	66543980	C	T	C	0.19	0	12310	0.999	0.485	0.105	3.52E-06	3829.657
rs55731089	7	66520438	C	T	T	0.19	0	12310	0.999	-0.485	0.105	3.53E-06	3827.315
rs58756282	7	66584920	C	T	T	0.19	0	12310	1	-0.485	0.105	3.59E-06	3822.248
rs10224763	7	66586221	A	G	G	0.19	0	12310	1	-0.485	0.105	3.59E-06	3822.245
rs2049831	14	80289134	G	A	A	0.46	0	12309	0.998	-0.372	0.080	3.61E-06	6121.819
rs10249587	7	66523392	G	A	A	0.19	0	12310	0.999	-0.485	0.105	3.61E-06	3831.745
rs2154265	10	56305290	T	C	C	0.41	0	12310	0.988	0.383	0.083	3.62E-06	5974.417
rs10925309	1	237250487	G	C	C	0.01	0	12310	0.995	-1.739	0.375	3.62E-06	294.293
rs11314136	7	66519689	AT	A	A	0.19	0	12310	0.999	-0.485	0.105	3.64E-06	3827.223
rs1445962	5	50300969	T	G	G	0.03	0	12309	0.997	-1.219	0.263	3.65E-06	644.569
rs7793589	7	66608855	G	T	T	0.18	0	12310	0.997	-0.496	0.107	3.72E-06	3608.105
rs78316461	7	66513067	G	A	A	0.19	0	12310	0.999	-0.484	0.105	3.73E-06	3827.203
rs10259711	7	66518946	C	T	T	0.19	0	12310	0.999	-0.484	0.105	3.74E-06	3827.171
rs34157075	7	66512317	A	C	C	0.19	0	12310	0.999	-0.484	0.105	3.74E-06	3827.298
rs12154876	7	66563135	A	G	G	0.19	0	12310	0.999	-0.486	0.105	3.75E-06	3790.520
rs17438468	2	193203685	C	T	C	0.02	0	12310	0.97	1.339	0.290	3.79E-06	481.810
rs2242648	14	80297210	G	C	C	0.46	0	12309	0.999	-0.371	0.080	3.84E-06	6119.945
rs6973836	7	66569208	G	A	A	0.19	0	12310	0.999	-0.484	0.105	3.86E-06	3809.351
rs79295862	5	50247859	T	C	C	0.02	0	12309	0.984	-1.523	0.330	3.87E-06	408.790
rs7783157	7	66574420	A	C	C	0.19	0	12310	0.998	-0.484	0.105	3.96E-06	3807.082
rs13243892	7	66576213	C	T	T	0.19	0	12310	0.999	-0.483	0.105	4E-06	3810.877
rs143925771	7	66578612	C	T	T	0.19	0	12310	0.999	-0.484	0.105	4.09E-06	3782.952
rs71535636	7	66512581	T	C	C	0.19	0	12310	0.999	-0.482	0.105	4.11E-06	3824.649
rs28465142	7	66611347	A	C	C	0.18	0	12310	0.999	-0.491	0.107	4.12E-06	3640.877

rs2140564	7	66590824	G	C	C	0.19	0	12310	0.999	-0.484	0.105	4.17E-06	3777.544
rs2960970	7	66574209	C	T	T	0.19	0	12310	1	-0.481	0.104	4.2E-06	3835.197
rs3857691	7	66608420	C	G	G	0.18	0	12310	1	-0.489	0.106	4.24E-06	3666.733
rs59247139	7	66574425	C	T	T	0.19	0	12310	0.999	-0.481	0.105	4.29E-06	3832.919
rs7099825	10	56304265	A	G	G	0.41	2	12310	1	0.379	0.082	4.32E-06	5959.839
rs73109514	5	50306261	G	C	C	0.03	0	12309	0.994	-1.222	0.266	4.39E-06	631.390
rs10262781	7	66620160	C	T	T	0.18	0	12310	1	-0.489	0.106	4.39E-06	3664.474
rs7350002	7	66620603	G	A	A	0.18	0	12310	1	-0.489	0.106	4.39E-06	3664.473
rs7792212	7	66621143	G	A	A	0.18	0	12310	1	-0.489	0.106	4.4E-06	3664.471
rs11004372	10	56304691	A	G	G	0.41	0	12310	0.995	0.380	0.083	4.40E-06	5958.309
rs35122750	7	66607147	A	G	G	0.18	0	12310	0.999	-0.490	0.107	4.43E-06	3635.922
rs9690120	7	66618358	G	A	A	0.18	0	12310	0.999	-0.489	0.106	4.43E-06	3664.976
rs10825349	10	56303722	A	G	G	0.41	0	12310	0.995	0.380	0.083	4.49E-06	5942.501
rs2004237	19	8209194	T	C	C	0.31	0	12310	0.995	0.399	0.087	4.49E-06	5282.771
rs6978918	7	66614462	T	C	C	0.18	2	12310	1	-0.488	0.106	4.53E-06	3667.336
rs10925310	1	237251005	T	C	C	0.01	2	12310	1	-1.693	0.370	4.64E-06	302.197
rs2687052	7	66621824	A	G	G	0.18	0	12310	0.998	-0.489	0.107	4.7E-06	3644.115
rs7809649	7	66602947	A	G	G	0.19	0	12310	0.998	-0.482	0.105	4.73E-06	3767.027
rs27276	5	50243725	G	A	G	0.02	0	12309	0.996	1.402	0.307	5.06E-06	459.655
rs113086330	5	50230664	C	T	T	0.02	0	12309	0.995	-1.472	0.323	5.11E-06	422.258
rs28888140	7	66593134	T	C	C	0.19	0	12310	1	-0.477	0.105	5.16E-06	3819.527
rs10274580	7	66592378	C	A	A	0.19	0	12310	1	-0.477	0.105	5.17E-06	3819.475
rs60910884	7	66598251	C	T	T	0.19	0	12310	1	-0.477	0.105	5.17E-06	3819.469
rs10233183	7	66597207	C	T	T	0.19	0	12310	1	-0.477	0.105	5.17E-06	3819.469
rs149883819	7	66600352	C	CA	CA	0.19	0	12310	1	-0.477	0.105	5.17E-06	3819.421
rs10244331	7	66622569	G	A	A	0.18	0	12310	0.999	-0.485	0.106	5.2E-06	3664.322
rs6603149	19	8213231	A	G	G	0.38	2	12310	1	0.376	0.083	5.59E-06	5803.442
rs1506452	1	71781585	A	G	G	0.32	2	12310	1	0.397	0.088	5.70E-06	5340.521
rs12751629	1	71793221	C	A	C	0.32	0	12310	1	-0.397	0.088	5.76E-06	5340.263
rs58448907	7	66595583	A	G	G	0.19	0	12310	0.999	-0.477	0.105	5.77E-06	3776.882
rs200905081	7	66610751	G	GT	GT	0.18	0	12310	0.998	-0.485	0.107	5.94E-06	3612.222
rs77219363	20	24489072	C	CCAGGCT GATCT	C	0.03	0	12310	0.814	1.119	0.247	5.96E-06	663.520
rs7793104	7	66621061	C	T	T	0.18	0	12310	0.999	-0.483	0.107	6.15E-06	3619.882
rs7776751	7	66608570	A	G	G	0.18	0	12310	0.999	-0.483	0.107	6.21E-06	3619.908
rs34457100	5	50170509	T	TA	T	0.02	0	12309	0.978	1.485	0.329	6.28E-06	410.341
rs144669467	3	98857716	CT	C	CT	0.19	0	12310	0.987	-0.465	0.103	6.32E-06	3682.868
rs7003790	8	59105992	C	T	T	0.03	0	12309	0.997	-1.024	0.227	6.33E-06	811.622

rs8127353	21	44076975	G	T	T	0.02	2	12309	1	-1.317	0.292	6.35E-06	479.287
rs3729908	16	24231248	T	C	T	0.07	0	12310	0.949	0.721	0.160	6.56E-06	1587.213
rs80269587	7	109709947	C	T	C	0.01	0	12310	0.94	1.747	0.388	6.7E-06	264.329
rs12561925	1	71813142	C	G	G	0.32	0	12310	0.994	0.394	0.088	6.75E-06	5364.009
rs2341717	3	98913821	A	G	A	0.21	0	12310	0.999	-0.444	0.099	6.79E-06	4044.402
rs73676501	7	7090025	T	A	A	0.02	0	12310	0.995	-1.529	0.340	6.84E-06	365.544
rs75361129	5	118250360	C	T	T	0.01	0	12310	0.996	-1.663	0.370	6.95E-06	316.398
rs150229484	11	70983910	CCA	C	C	0.12	0	12310	0.83	-0.631	0.140	6.99E-06	2125.299
rs148893024	11	113663454	T	A	A	0.01	0	12309	0.996	-1.781	0.396	7.03E-06	276.713
rs2242642	14	80286306	C	G	G	0.47	0	12309	0.998	-0.361	0.080	7.22E-06	6128.027
rs115139710	5	118262011	G	A	A	0.01	0	12310	0.996	-1.660	0.370	7.25E-06	316.239
rs115837370	9	135886735	G	A	A	0.01	0	12310	0.924	-1.925	0.429	7.40E-06	229.301
rs77669066	5	50223773	A	G	G	0.02	0	12309	0.998	-1.357	0.303	7.69E-06	473.446
rs17091578	14	32388774	C	G	G	0.27	0	12310	0.979	-0.408	0.091	7.84E-06	4845.766
rs73922237	19	8206553	C	T	C	0.36	0	12310	0.993	-0.375	0.084	7.85E-06	5645.090
rs7007843	8	59111965	G	T	T	0.04	0	12309	0.999	-0.941	0.211	7.92E-06	942.655
rs77927049	14	81543731	G	A	A	0.02	0	12309	0.998	1.456	0.326	7.92E-06	404.976
rs201573719	11	113668782	ATGC	A	A	0.01	0	12309	0.992	-1.767	0.396	7.97E-06	278.861
rs56345969	17	78171236	G	A	A	0.03	0	12310	0.933	1.175	0.263	8.05E-06	590.029
rs145115978	3	98897408	T	TAAAG	T	0.21	0	12310	0.999	-0.440	0.099	8.12E-06	4050.468
rs62346660	4	146233605	A	G	G	0.03	0	12310	0.806	-1.175	0.263	8.12E-06	587.068
rs77893100	5	50223043	C	G	G	0.02	0	12309	0.997	-1.353	0.303	8.20E-06	473.508
rs3958407	5	50236508	C	T	T	0.02	0	12309	0.935	-1.328	0.298	8.30E-06	499.257
rs11710896	3	98950647	C	A	A	0.19	0	12310	0.999	0.457	0.103	8.38E-06	3728.466
rs10501248	11	41083620	C	A	A	0.42	2	12310	1	-0.360	0.081	8.44E-06	6016.137
rs73149623	3	98938539	G	A	A	0.19	0	12310	0.997	0.457	0.103	8.56E-06	3725.718
rs10264133	7	27231097	C	T	T	0.02	0	12310	0.989	-1.277	0.287	8.71E-06	518.575
rs4985364	16	70806674	C	T	C	0.17	0	12310	0.996	0.479	0.108	8.74E-06	3530.366
rs143528581	13	66676730	AAAT	A	A	0.02	0	12310	0.992	1.264	0.284	8.77E-06	501.610
rs2242646	14	80288888	A	G	G	0.47	2	12309	1	-0.357	0.080	8.78E-06	6130.353
rs1092312	3	98908158	G	A	G	0.21	0	12310	1	-0.438	0.099	9.10E-06	4048.893
rs10768363	11	38257707	C	T	C	0.08	0	12310	0.999	0.697	0.157	9.42E-06	1889.938
rs62273517	3	111225082	G	A	A	0.07	0	12310	0.967	-0.707	0.160	9.44E-06	1535.633
rs4928154	3	98899033	C	A	C	0.21	2	12310	1	-0.436	0.099	9.62E-06	4071.562
rs774972	3	98902911	C	T	C	0.21	2	12310	1	-0.436	0.099	9.62E-06	4071.562
rs74317030	5	50221498	A	T	T	0.02	0	12309	0.997	-1.343	0.304	9.64E-06	473.664

12:102270520:T:C	12	102270520	T	C	C	0.01	0	12310	0.881	-1.665	0.376	9.67E-06	297.943
12:91777215:A:AGGGAGTTGCTTGAGTTGTCAGC	12	91777215	A	AGGGAGTTGCTTGAGTTGTCA	AGGGAGTTGCTTGAGTTGTCA	0.10	0	12310	0.989	0.586	0.133	9.68E-06	2216.235
rs1082507	3	98916453	C	T	C	0.21	0	12310	1	-0.436	0.099	9.68E-06	4044.209
rs140015087	17	27187143	G	A	A	0.04	0	12310	0.997	0.873	0.197	9.70E-06	976.176
rs1082509	3	98916822	T	C	T	0.21	0	12310	1	-0.436	0.099	9.71E-06	4044.096
7:66562845:AT:A	7	66562845	AT	A	A	0.27	0	12310	0.877	-0.440	0.099	9.77E-06	4381.671
3:98914294:T:TACC	3	98914294	T	TACC	T	0.21	0	12310	0.999	-0.436	0.099	9.79E-06	4045.996
12:108591180:AG:A	12	108591180	AG	A	AG	0.45	0	12310	0.997	0.356	0.081	9.82E-06	6093.300
rs1066358	3	98911343	A	G	A	0.21	0	12310	0.999	-0.436	0.099	9.84E-06	4045.500
rs1066359	3	98910719	A	G	A	0.21	0	12310	0.999	-0.436	0.099	9.84E-06	4045.622
rs1066360	3	98910706	C	T	C	0.21	0	12310	0.999	-0.436	0.099	9.84E-06	4045.625
rs1066361	3	98910395	C	A	C	0.21	0	12310	0.999	-0.436	0.099	9.85E-06	4045.687
rs1082510	3	98916842	G	A	G	0.21	0	12310	1	-0.436	0.099	9.86E-06	4044.380
rs1082512	3	98917002	T	G	T	0.21	0	12310	1	-0.436	0.099	9.86E-06	4044.346
rs1066364	3	98906623	A	G	A	0.21	0	12310	1	-0.436	0.099	9.90E-06	4046.427
rs1066365	3	98906197	C	A	C	0.21	0	12310	1	-0.436	0.099	9.90E-06	4046.510
rs1066366	3	98905942	G	T	G	0.21	0	12310	1	-0.436	0.099	9.91E-06	4046.560
rs76128500	3	21197126	C	T	T	0.04	0	12310	0.999	-0.909	0.206	9.99E-06	1036.622

CHR=chromosome. In the geno. (genotyping) column, 0=imputed SNP and 2=genotyped SNP. Info refers to info score for imputation (indicating imputation quality); all imputed SNPs had info scores ≥ 0.80. AlleleA is the tested allele. MAF is the estimated minor allele frequency and is ≥ 0.01 for all SNPs. Position is given in genome build GRCh37/hg19. effN, or the "effective minor allele count" of a variant, is defined as 2p(1-p)Nv, where p is the estimated minor allele frequency, N is the sample size, and v is "oevar", a measure of imputation accuracy. If a SNP is genotyped, then oevar =1. For imputed genotypes, oevar is the ratio between the observed variance of the genotype dosage to the expected binomial variance, based on the estimated minor allele frequency p; effN is >30 for all SNPs.

Supplemental Table 5: Replication results from top loci on chromosome 7: rs34208798

A. Adjusting for medication use

	SNP	CHR	position	alleleA	alleleB	MAF	minor allele	geno.	n	Beta	SE	pval
discovery	rs34208798	7	66518851	G	A	0.188	A	I	12310	-0.51	0.11	1.47E-06
Army NSS1	rs34208798	7	66518851	A	G	0.193	A	I	1385	0.09	0.17	0.612
Army NSS2	rs34208798	7	66518851	A	G	0.190	A	I	451	-0.02	0.31	0.954
Army PPDS	rs34208798	7	66518851	A	G	0.187	A	I	1525	-0.14	0.16	0.383
MESA	rs34208798	7	66518851	A	G	0.165	A	I	1449	-0.03	0.04	0.459
WHI	rs10242790	7	66516641	A	G	0.219	A	I	3138	-0.33	0.11	0.002
Meta Analysis				A	G				7948	-0.06	0.04	0.084

B. Excluding medication users

	SNP	CHR	position	alleleA	alleleB	MAF	minor allele	geno	n	Beta	SE	pval
discovery	rs34208798	7	66518851	G	A	0.186	A	I	11486	-0.52	0.10	1.87E-07
Army NSS1	rs34208798	7	66518851	A	G	0.193	A	I	1348	0.09	0.17	0.586
Army NSS2	rs34208798	7	66518851	A	G	0.189	A	I	429	-0.07	0.31	0.824
Army PPDS	rs34208798	7	66518851	A	G	0.185	A	I	1425	-0.14	0.16	0.396
MESA	rs34208798	7	66518851	A	G	0.164	A	I	1362	-0.04	0.05	0.380
WHI	rs10242790	7	66516641	A	G	0.223	A	I	2745	-0.27	0.10	0.009
Meta Analysis				A	G				7309	-0.08	0.04	0.06

CHR=chromosome. In the geno. (genotyping) column, G=genotyped and I=imputed. All imputed SNPs had info scores (indicating imputation quality) >0.83. AlleleA is the tested allele. The Army STARRs dataset was comprised of three different cohorts: the New Soldiers Study 1, the New Soldiers Study 2, and the Post Deployment Study. The SNP identified in the discovery analysis and carried forward to the replication (rs34208798) was neither genotyped nor imputed in WHI so we used rs10242790 as a highly-correlated proxy. The imputation values for all cohorts were excellent (Army NSS1=1.01; Army NSS2=1.07; Army PPDS=0.97; WHI=0.83; MESA=0.98).

Supplemental Table 6: Replication results from top loci on chromosome 19: rs2004237

A. Adjusting for medication use

	SNP	CHR	position	alleleA	alleleB	MAF	minor allele	geno.	n	Beta	SE	pval
discovery	rs2004237	19	8209194	T	C	0.312	C	I	12310	0.40	0.09	4.49E-06
Army NSS1	rs2004237	19	8209194	T	C	0.286	C	I	1385	-0.01	0.16	0.973
Army NSS2	rs2004237	19	8209194	T	C	0.318	C	I	451	0.239	0.29	0.413
Army PPDS	rs2004237	19	8209194	T	C	0.295	C	I	1525	-0.08	0.14	0.549
MESA	rs2004237	19	8209194	T	C	0.280	C	I	1449	-0.01	0.06	0.820
WHI	rs7252584	19	8207241	C	G	0.169	G	I	3138	-0.05	0.10	0.650
Meta Analysis				T	C				7948	-0.020	0.05	0.668

B. Excluding medication users

	SNP	CHR	position	alleleA	alleleB	MAF	minor allele	geno	n	Beta	SE	pval
discovery	rs2004237	19	8209194	T	C	0.313	C	I	11486	0.45	0.08	7.54E-08
Army NSS1	rs2004237	19	8209194	T	C	0.285	C	I	1348	0.01	0.16	0.949
Army NSS2	rs2004237	19	8209194	T	C	0.328	C	I	429	0.24	0.29	0.401
Army PPDS	rs2004237	19	8209194	T	C	0.293	C	I	1425	-0.08	0.14	0.567
MESA	rs2004237	19	8209194	T	C	0.280	C	I	1362	-0.02	0.07	0.770
WHI	rs7252584	19	8207241	C	G	0.167	G	I	2745	0.03	0.10	0.777
Meta Analysis				T	C				7309	-0.005	0.05	0.924

CHR=chromosome. In the geno. (genotyping) column, G=genotyped and I=imputed. All imputed SNPs had info scores (indicating imputation quality) >0.37. AlleleA is the tested allele. The Army STARRs dataset was comprised of three different cohorts: the New Soldiers Study 1, the New Soldiers Study 2, and the Post Deployment Study. Note: The SNP identified in the discovery analysis and carried forward to the replication (rs2004237) was neither genotyped nor imputed in WHI so we used rs7252584 as a highly-correlated proxy. The imputation values for all cohorts was good (Army NSS1=0.72; Army NSS2=0.67; Army PPDS=0.71; WHI=1.02-1.03; MESA=0.37).

Supplemental Table 7: Genome-wide association study (GWAS) results for the top loci ($p<1x10^{-5}$) with the depressive symptom score, after adjusting for medication use, among females

SNP	CHR	position	alleleA	alleleB	minor allele	MAF	geno	n	info	Beta	SE	pval	effN
rs72662446	8	59113186	C	T	T	0.03	2	7263	1	-1.85	0.32	6.36E-09	468.807
rs9599044	13	66494976	T	A	A	0.03	0	7264	0.961	1.87	0.36	2.16E-07	353.893
rs139628768	6	154761127	C	A	A	0.01	0	7264	0.911	-3.35	0.65	2.82E-07	108.356
rs112390938	7	156779166	C	T	C	0.01	0	7264	0.841	3.12	0.62	6.01E-07	113.645
rs953628	3	98838914	G	T	T	0.17	2	7264	1	0.72	0.15	6.96E-07	2087.454
rs5972903	X	33619774	T	C	C	0.46	0	7261	0.993	-0.55	0.11	9.19E-07	3603.683

CHR=chromosome. In the geno. (genotyping) column, 0=imputed SNP and 2=genotyped SNP. Info refers to info score for imputation (indicating imputation quality); all imputed SNPs had info scores ≥ 0.80. AlleleA is the tested allele. MAF is the estimated minor allele frequency and is ≥ 0.01 for all SNPs. Position is given in genome build GRCh37/hg19. effN, or the "effective minor allele count" of a variant, is defined as 2p(1-p)Nv, where p is the estimated minor allele frequency, N is the sample size, and v is "oevar", a measure of imputation accuracy. If a SNP is genotyped, then oevar =1. For imputed genotypes, oevar is the ratio between the observed variance of the genotype dosage to the expected binomial variance, based on the estimated minor allele frequency p; effN is >30 for all SNPs.

Supplemental Table 8: Genome-wide association study (GWAS) results for the top loci ($p<1x10^{-6}$) with the depressive symptom score, after excluding medication users, among females

SNP	CHR	position	alleleA	alleleB	minor allele	MAF	geno	n	info	Beta	SE	pval	effN
rs72662446	8	59113186	C	T	T	0.03	2	6653	1	-1.69	0.31	7.48E-08	409.553
rs8127353	21	44076975	G	T	T	0.02	2	6654	1	-2.04	0.40	2.32E-07	252.037
rs789539	11	131578101	C	T	C	0.15	0	6653	0.991	-0.79	0.15	2.88E-07	1679.723
rs2049285	3	182591147	T	G	T	0.45	0	6654	1	-0.54	0.11	3.60E-07	3295.993
rs139642111	3	29121696	A	G	G	0.03	0	6654	0.996	-1.57	0.31	4.06E-07	382.378
rs11087469	20	24489072	C	CCAGGCT GATCT	C	0.03	0	6654	0.814	1.67	0.33	4.83E-07	360.073
rs189109527	7	158944876	G	A	A	0.02	0	6654	0.47	-3.13	0.62	5.03E-07	101.289
rs5841036	20	24502210	T	TG	T	0.02	0	6654	0.9	2.12	0.42	5.30E-07	221.063
rs2695833	11	131568375	C	T	T	0.13	2	6653	1	0.80	0.16	6.34E-07	1515.416
rs78623934	5	43232851	A	G	G	0.01	0	6654	0.976	-2.90	0.58	6.43E-07	122.677
rs2658825	11	131545637	T	C	T	0.15	0	6653	0.976	-0.76	0.15	7.87E-07	1731.266
rs675071	3	182604826	T	C	T	0.45	2	6654	1	-0.53	0.11	8.32E-07	3289.652

CHR=chromosome. In the geno. (genotyping) column, 0=imputed SNP and 2=genotyped SNP. Info refers to info score for imputation (indicating imputation quality); all imputed SNPs had info scores ≥ 0.80. AlleleA is the tested allele. MAF is the estimated minor allele frequency and is ≥ 0.01 for all SNPs. Position is given in genome build GRCh37/hg19. effN, or the "effective minor allele count" of a variant, is defined as 2p(1-p)Nv, where p is the estimated minor allele frequency, N is the sample size, and v is "oevar", a measure of imputation accuracy. If a SNP is genotyped, then oevar =1. For imputed genotypes, oevar is the ratio between the observed variance of the genotype dosage to the expected binomial variance, based on the estimated minor allele frequency p; effN is >30 for all SNPs.

Supplemental Table 9: Genome-wide association study (GWAS) results for the top loci ($p<1x10^{-5}$) with the depressive symptom score, after adjusting for medication use, among males

SNP	CHR	position	alleleA	alleleB	minor allele	MAF	geno	n	info	Beta	SE	pval	effN
rs111365740	4	122586829	C	G	G	0.03	0	5046	0.995	-1.86	0.34	3.70E-08	279.306
rs9709324	17	81084820	C	T	T	0.03	0	5046	0.763	-2.08	0.38	4.20E-08	231.434
rs113403132	19	44913426	G	A	A	0.04	0	5046	0.981	-1.43	0.27	1.33E-07	419.848
rs139198916	17	81084996	T	C	C	0.04	0	5046	0.778	-1.70	0.33	1.83E-07	330.390
rs7256562	19	44902338	G	A	A	0.04	2	5046	1	-1.35	0.27	5.15E-07	420.816
rs112305520	8	81668343	C	CA	CA	0.12	0	5046	0.917	0.90	0.18	6.31E-07	1022.800
rs149998181	7	7092566	C	T	T	0.01	0	5046	0.984	-2.56	0.52	8.38E-07	120.364

CHR=chromosome. In the geno. (genotyping) column, 0=imputed SNP and 2=genotyped SNP. Info refers to info score for imputation (indicating imputation quality); all imputed SNPs had info scores ≥ 0.80. AlleleA is the tested allele. MAF is the estimated minor allele frequency and is ≥ 0.01 for all SNPs. Position is given in genome build GRCh37/hg19. effN, or the "effective minor allele count" of a variant, is defined as $2p(1-p)Nv$, where p is the estimated minor allele frequency, N is the sample size, and v is "oevar", a measure of imputation accuracy. If a SNP is genotyped, then oevar =1. For imputed genotypes, oevar is the ratio between the observed variance of the genotype dosage to the expected binomial variance, based on the estimated minor allele frequency p; effN is >30 for all SNPs.

Supplemental Table 10: Genome-wide association study (GWAS) results for the top loci ($p<1x10^{-6}$) with the depressive symptom score, after excluding medication users, among males

SNP	CHR	position	alleleA	alleleB	minor allele	MAF	geno	n	info	Beta	SE	pval	effN
rs113403132	19	44913426	G	A	A	0.04	0	4832	0.981	-1.45	0.25	7.74E-09	400.873
rs6993028	8	20875758	G	A	A	0.02	2	4832	1	-2.01	0.35	1.27E-08	208.305
rs144850488	19	44893040	G	A	A	0.05	0	4832	0.922	-1.43	0.26	2.69E-08	390.196
rs17800303	19	44902416	C	A	A	0.05	2	4832	1	-1.35	0.24	3.59E-08	419.967
rs73039936	19	44890685	T	G	G	0.07	0	4832	0.76	-1.24	0.23	1.26E-07	460.609
rs62319821	4	122621940	G	C	C	0.03	0	4832	0.991	-1.68	0.32	1.39E-07	261.573
rs139991167	12	133795766	G	T	T	0.02	0	4832	0.97	-2.15	0.41	1.76E-07	164.899
rs2087144	2	78006805	G	A	A	0.22	2	4832	1	-0.62	0.12	4.32E-07	1684.390
rs202022310	15	70749217	GTTTA	G	G	0.04	0	4832	0.852	-1.42	0.28	4.72E-07	319.373
rs2289935	12	65462953	G	C	C	0.11	0	4832	0.996	-0.80	0.16	5.14E-07	953.358
rs114347092	17	17813119	G	A	A	0.02	0	4832	0.986	-1.79	0.36	5.85E-07	208.250
rs2718851	3	129769827	C	T	C	0.02	0	4832	0.827	2.01	0.40	6.00E-07	163.998
rs11276099	4	57127048	TATCCATCCATC	T	T	0.36	0	4832	0.939	-0.54	0.11	8.32E-07	2117.413
rs281469	2	46405834	C	T	C	0.15	2	4832	1	-0.72	0.15	9.83E-07	1240.824

CHR=chromosome. In the geno. (genotyping) column, 0=imputed SNP and 2=genotyped SNP. Info refers to info score for imputation (indicating imputation quality); all imputed SNPs had info scores ≥ 0.80. AlleleA is the tested allele. MAF is the estimated minor allele frequency and is ≥ 0.01 for all SNPs. Position is given in genome build GRCh37/hg19. effN, or the "effective minor allele count" of a variant, is defined as 2p(1-p)Nv, where p is the estimated minor allele frequency, N is the sample size, and v is "oevar", a measure of imputation accuracy. If a SNP is genotyped, then oevar =1. For imputed genotypes, oevar is the ratio between the observed variance of the genotype dosage to the expected binomial variance, based on the estimated minor allele frequency p; effN is >30 for all SNPs.

Supplemental Table 11: Replication results from top loci on chromosome 8 in females: rs72662446

A. Adjusting for medication use

	SNP	CHR	position	alleleA	alleleB	MAF	minor allele	geno.	n	Beta	SE	pval
discovery	rs72662446	8	59113186	C	T	0.033	T	G	7263	-1.849	0.32	6.36E-09
Army NSS1	rs72662446	8	59113186	C	T	0.047	T	I	246	0.209	0.74	0.778
Army NSS2	rs72662446	8	59113186	C	T	0.010	T	I	108	NA	NA	NA
Army PPDS	rs72662446	8	59113186	C	T	0.050	T	I	112	1.456	1.26	0.249
MESA	rs72662446	8	59113186	C	T	0.032	T	I	748	-0.119	0.31	0.699
WHI	rs55719516	8	59114301	T	C	0.032	C	I	3138	0.202	0.23	0.379
Meta Analysis				C	T				4244	0.1221	0.18	0.491

B. Excluding medication users

	SNP	CHR	position	alleleA	alleleB	MAF	minor allele	geno	n	Beta	SE	pval
discovery	rs72662446	8	59113186	C	T	0.032	T	G	6653	-1.689	0.31	7.48E-08
Army NSS1	rs72662446	8	59113186	C	T	0.043	T	I	232	-0.076	0.76	0.920
Army NSS2	rs72662446	8	59113186	C	T	0.010	T	I	104	-1.923	2.55	0.452
Army PPDS	rs72662446	8	59113186	C	T	0.045	T	I	100	0.337	1.10	0.760
MESA	rs72662446	8	59113186	C	T	0.030	T	I	696	-0.285	0.33	0.388
WHI	rs55719516	8	59114301	T	C	0.032	C	I	2745	0.353	0.23	0.117
Meta Analysis				C	T				3877	0.127	0.18	0.481

CHR=chromosome. In the geno. (genotyping) column, G=genotyped and I=imputed. All imputed SNPs had info scores (indicating imputation quality) >0.95. AlleleA is the tested allele. The Army STARRs dataset was comprised of three different cohorts: the New Soldiers Study 1, the New Soldiers Study 2, and the Post Deployment Study. The SNP identified in the discovery analysis and carried forward to the replication (rs72662446) was neither genotyped nor imputed in WHI, so we used rs55719516 as a highly-correlated proxy. Due to low MAF, estimates for the Army NSS2 are not present for the analysis adjusting for medication users. The imputation values for all cohorts were excellent (Army NSS1=1.04-1.06; Army NSS2= 0.95; Army PPDS=0.95; WHI=0.97; MESA=0.98).

Supplemental Table 12: Replication results from top loci on chromosome 17 in males: rs9709324

A. Adjusting for medication use

	SNP	CHR	position	alleleA	alleleB	MAF	minor allele	geno.	n	Beta	SE	pval
discovery	rs9709324	17	81084820	C	T	0.030	T	I	5046	-2.076	0.38	4.20E-08
Army NSS1	rs9709324	17	81084820	C	T	0.022	T	I	1139	-0.714	0.70	0.311
Army NSS2	rs9709324	17	81084820	C	T	0.019	T	I	343	-0.753	1.51	0.619
Army PPDS	rs9709324	17	81084820	C	T	0.019	T	I	1413	-0.282	0.72	0.694
MESA	rs9709324	17	81084820	C	T	0.021	T	I	702	0.138	0.76	0.856
Meta Analysis				C	T				3597	-0.341	0.40	0.398

B. Excluding medication users

	SNP	CHR	position	alleleA	alleleB	MAF	minor allele	geno	n	Beta	SE	pval
discovery	rs9709324	17	81084820	C	T	0.028	T	I	4832	-1.609	0.36	6.68E-06
Army NSS1	rs9709324	17	81084820	C	T	0.022	T	I	1116	-0.595	0.69	0.388
Army NSS2	rs9709324	17	81084820	C	T	0.019	T	I	325	-0.266	1.42	0.852
Army PPDS	rs9709324	17	81084820	C	T	0.019	T	I	1325	-0.132	0.65	0.839
MESA	rs9709324	17	81084820	C	T	0.019	T	I	667	0.154	0.70	0.826
Meta Analysis				C	T				3433	-0.197	0.38	0.602

CHR=chromosome. In the geno. (genotyping) column, G=genotyped and I=imputed. All imputed SNPs had info scores (indicating imputation quality) >0.29. AlleleA is the tested allele. The Army STARRs dataset was comprised of three different cohorts: the New Soldiers Study 1, the New Soldiers Study 2, and the Post Deployment Study. The imputation values for most cohorts were acceptable (Army NSS1=0.56; Army NSS2= 0.62-0.64; Army PPDS=0.56; MESA=0.29).

Supplemental Table 13: Replication results from top loci on chromosome 8 in males: rs6993028

A. Adjusting for medication use

	SNP	CHR	position	alleleA	alleleB	MAF	minor allele	geno.	n	Beta	SE	pval
discovery	rs6993028	8	20875758	G	A	0.022	A	G	5046	-1.812	0.38	2.18E-06
Army NSS1	rs6993028	8	20875758	G	A	0.037	A	I	1139	0.098	0.44	0.824
Army NSS2	rs6993028	8	20875758	G	A	0.037	A	I	343	-1.865	1.03	0.070
Army PPDS	rs6993028	8	20875758	G	A	0.029	A	I	1413	-0.307	0.45	0.494
MESA	rs6993028	8	20875758	G	A	0.018	A	G	702	0.124	0.42	0.768
Meta Analysis				G	A				3597	-0.124	0.24	0.614

B. Excluding medication users

	SNP	CHR	position	alleleA	alleleB	MAF	minor allele	geno	n	Beta	SE	pval
discovery	rs6993028	8	20875758	G	A	0.022	A	G	4832	-2.013	0.35	1.27E-08
Army NSS1	rs6993028	8	20875758	G	A	0.037	A	I	1116	0.159	0.43	0.713
Army NSS2	rs6993028	8	20875758	G	A	0.037	A	I	325	-1.487	0.97	0.125
Army PPDS	rs6993028	8	20875758	G	A	0.029	A	I	1325	-0.166	0.40	0.682
MESA	rs6993028	8	20875758	G	A	0.017	A	G	667	-0.046	0.41	0.910
Meta Analysis				G	A				3433	-0.109	0.23	0.638

CHR=chromosome. In the geno. (genotyping) column, G=genotyped and I=imputed. All imputed SNPs had info scores (indicating imputation quality) >0.67. AlleleA is the tested allele. The Army STARRs dataset was comprised of three different cohorts: the New Soldiers Study 1, the New Soldiers Study 2, and the Post Deployment Study. The imputation values for all cohorts were good (Army NSS1=0.81; Army NSS2= 0.67; Army PPDS=0.89).

Supplemental Table 14: Replication results from top loci on chromosome 19 in males: rs144850488

A. Adjusting for medication use

	SNP	CHR	position	alleleA	alleleB	MAF	minor allele	geno.	n	Beta	SE	pval
discovery	rs144850488	19	44893040	G	A	0.045	A	I	5046	-1.306	0.28	2.36E-06
Army NSS1	rs144850488	19	44893040	G	A	0.049	A	I	1139	-0.670	0.39	0.083
Army NSS2	rs144850488	19	44893040	G	A	0.045	A	I	343	0.809	0.88	0.357
Army PPDS	rs144850488	19	44893040	G	A	0.047	A	I	1413	0.115	0.36	0.749
MESA	rs144850488	19	44893040	G	A	0.039	A	I	702	-0.156	0.36	0.667
Meta Analysis				G	A				3597	-0.158	0.21	0.446

B. Excluding medication users

	SNP	CHR	position	alleleA	alleleB	MAF	minor allele	geno	n	Beta	SE	pval
discovery	rs144850488	19	44893040	G	A	0.045	A	I	4832	-1.426	0.26	2.69E-08
Army NSS1	rs144850488	19	44893040	G	A	0.050	A	I	1116	-0.555	0.38	0.141
Army NSS2	rs144850488	19	44893040	G	A	0.045	A	I	325	0.863	0.84	0.307
Army PPDS	rs144850488	19	44893040	G	A	0.046	A	I	1325	0.044	0.32	0.893
MESA	rs144850488	19	44893040	G	A	0.036	A	I	667	-0.230	0.37	0.508
Meta Analysis				G	A				3433	-0.152	0.20	0.443

CHR=chromosome. In the geno. (genotyping) column, G=genotyped and I=imputed. All imputed SNPs had info scores (indicating imputation quality) >0.71. AlleleA is the tested allele. The Army STARRs dataset was comprised of three different cohorts: the New Soldiers Study 1, the New Soldiers Study 2, and the Post Deployment Study. The imputation values for all cohorts were good (Army NSS1=0.84; Army NSS2= 0.79; Army PPDS=0.88; MESA=0.71).

Supplemental Table 15: Replication results from top loci on chromosome 19 in males: rs113403132

A. Adjusting for medication use

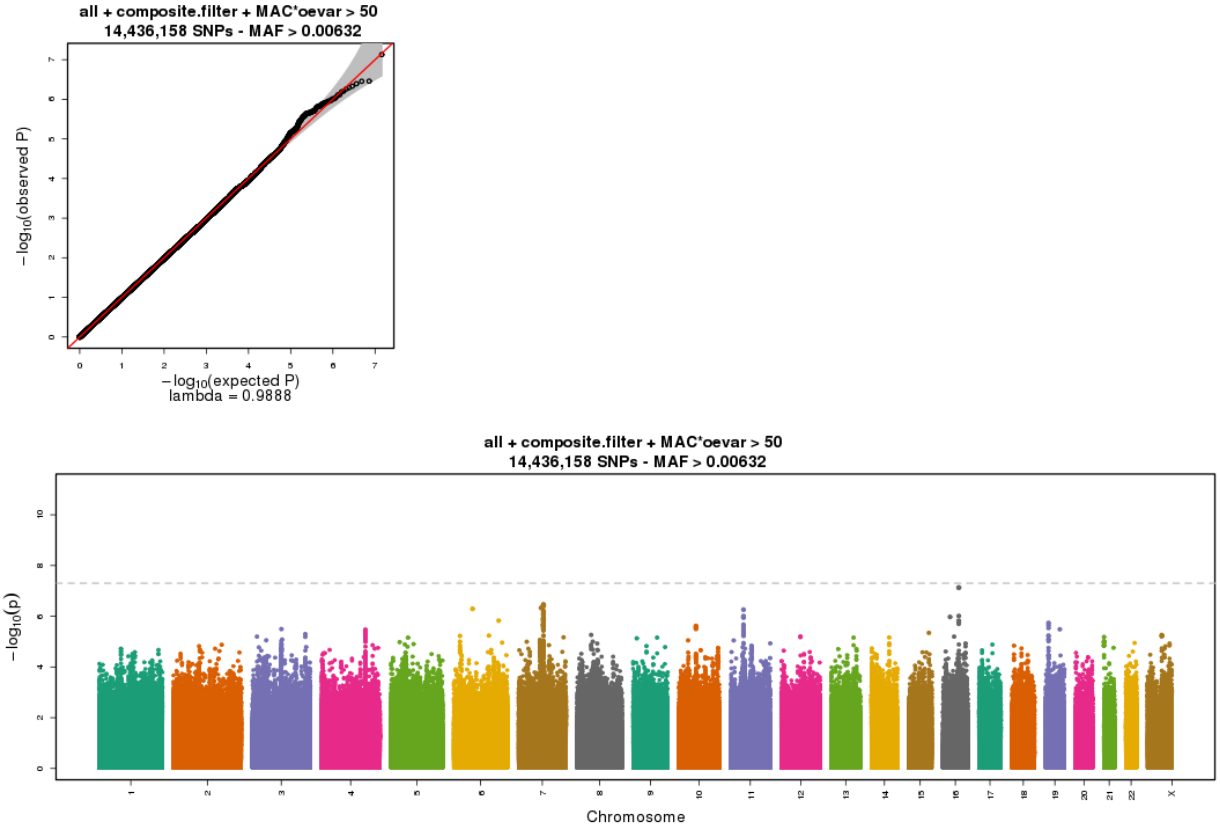
	SNP	CHR	position	alleleA	alleleB	MAF	minor allele	geno.	n	Beta	SE	pval
discovery	rs113403132	19	44913426	G	A	0.044	A	I	5046	-1.427	0.27	1.33E-07
Army NSS1	rs113403132	19	44913426	G	A	0.046	A	G	1139	-0.651	0.37	0.081
Army NSS2	rs113403132	19	44913426	G	A	0.040	A	G	343	1.421	0.88	0.107
Army PPDS	rs113403132	19	44913426	G	A	0.044	A	G	1413	-0.078	0.35	0.824
MESA	rs113403132	19	44913426	G	A	0.037	A	I	702	0.024	0.39	0.951
Meta Analysis				G	A				3597	-0.146	0.21	0.482

B. Excluding medication users

	SNP	CHR	position	alleleA	alleleB	MAF	minor allele	geno	n	Beta	SE	pval
discovery	rs113403132	19	44913426	G	A	0.044	A	I	4832	-1.450	0.25	7.74E-09
Army NSS1	rs113403132	19	44913426	G	A	0.047	A	G	1116	-0.550	0.36	0.132
Army NSS2	rs113403132	19	44913426	G	A	0.037	A	G	325	1.353	0.86	0.119
Army PPDS	rs113403132	19	44913426	G	A	0.044	A	G	1325	-0.102	0.32	0.748
MESA	rs113403132	19	44913426	G	A	0.036	A	I	667	0.024	0.38	0.949
Meta Analysis				G	A				3433	-0.126	0.20	0.523

CHR=chromosome. In the geno. (genotyping) column, G=genotyped and I=imputed. All imputed SNPs had info scores (indicating imputation quality) >0.66. AlleleA is the tested allele. The Army STARRs dataset was comprised of three different cohorts: the New Soldiers Study 1, the New Soldiers Study 2, and the Post Deployment Study. The imputation values for all cohorts was good (Army NSS1=0.95; Army NSS2= 0.89; Army PPDS=0.99; MESA=0.66).

Supplemental Figure 1. Quantile-quantile (QQ) plots and Manhattan plots for binary depressive symptoms score from the Hispanic Community Health Study/Study of Latinos



The quantile–quantile plots ("QQ-plots"), which present the observed by expected P-values on the -log10 scale, indicate conformity of the observed results to what would be expected under the null. In the Manhattan plots, the x-axis is the chromosomal position and the y-axis is the -log10 p-value for the association between each SNP and depressive case/control status derived. The dotted line shows the genome-wide significance level ($5x10^{-8}$). The displayed p-value corresponds to SNPs with effective N > 50.

Supplemental Table 16: Genome-wide association study (GWAS) results for the top loci ($p<1x10^{-6}$) with the with the binary depressive symptom

SNP	CHR	position	alleleA	alleleB	minor. allele	MAF	geno	n	info	Beta	OR	Beta SE	pval	effN
rs10611601	7	70044230	TAA	T	TAA	0.43	0	10478	0.849	-0.169	0.845	0.034	4.68E-07	4326.31
rs10250251	7	79209569	C	T	T	0.16	0	10478	0.998	0.207	1.230	0.042	7.70E-07	2886.814
rs10272118	7	79210117	T	C	C	0.17	0	10478	0.998	0.211	1.235	0.041	3.51E-07	2953.797
rs73375972	7	79219694	C	T	T	0.17	0	10478	0.999	0.210	1.234	0.041	4.05E-07	2938.585
rs10242135	7	79223076	A	T	T	0.17	0	10478	0.999	0.211	1.235	0.042	3.49E-07	2936.463
rs7796725	7	79223511	C	A	A	0.16	0	10478	0.999	0.206	1.229	0.042	8.73E-07	2867.075
rs4730938	7	79227068	T	C	C	0.16	0	10478	0.999	0.209	1.232	0.042	6.19E-07	2872.58
rs10254034	7	79231624	C	A	C	0.16	0	10478	0.998	-0.208	0.812	0.042	7.74E-07	2862.825
rs73375991	7	79232355	A	G	G	0.16	0	10478	0.998	0.206	1.229	0.042	9.46E-07	2864.113
rs201548423	7	79255146	TTA	T	TTA	0.21	0	10478	0.998	-0.192	0.825	0.039	6.52E-07	3463.486
rs10501248	11	41083620	C	A	A	0.43	2	10478	1	-0.154	0.857	0.031	5.49E-07	5123.614
rs7129748	11	41098364	T	A	T	0.46	0	10478	0.999	0.149	1.161	0.030	9.82E-07	5199.555
rs4442810	16	65676733	C	T	T	0.43	2	10478	1	0.161	1.175	0.033	9.78E-07	5129.04
rs12232405	16	65699931	A	G	A	0.43	0	10478	0.991	-0.178	0.837	0.033	7.43E-08	5138.293

The phenotype in this analysis was the untransformed original total depressive symptoms score, which did not consider psychiatric medication use. CHR=chromosome. In the geno. (genotyping) column, 0=imputed SNP and 2=genotyped SNP. Info refers to info score for imputation. AlleleA is the tested allele. Position is given in genome build GRCh37/hg19. effN, or the "effective minor allele count" of a variant, is defined as 2p(1-p)Nv, where p is the estimated minor allele frequency, N is the sample size, and v is "oevar", a measure of imputation accuracy. If a SNP is genotyped, then oevar =1. For imputed genotypes, oevar is the ratio between the observed variance of the genotype dosage to the expected binomial variance, based on the estimated minor allele frequency p.

Supplemental Table 17: Associations between GRSs constructed on three discovery GWAS and depressive symptom scores in the HCHS/SOL

Study	GRS p-threshold	Original depressive symptom score		Adjusting for medication use		Excluding medication users		Binary depressive symptom	
		β (95% CI)	P	β (95% CI)	P	β (95% CI)	P	OR (95% CI)	P
PGC & 23andme	P<0.05	0.007 (0.002,0.011)	0.005	0.008 (0.003,0.012)	0.002	0.006 (0.001,0.010)	0.013	1.001 (1.000,1.001)	0.002
PGC & 23andme	P<0.01	0.007 (0.002,0.012)	0.004	0.008 (0.003,0.013)	0.001	0.006 (0.001,0.011)	0.012	1.001 (1.000,1.001)	0.002
PGC & 23andme	**P<0.001**	**0.012 (0.006,0.017)**	**0.00004**	**0.013 (0.007,0.019)**	**0.00004**	**0.011 (0.005,0.017)**	**0.0001**	**1.001 (1.000,1.001)**	**0.0004**
PGC & 23andme	$P<10^{-4}$	0.018 (0.008,0.028)	0.001	0.018 (0.007,0.028)	0.001	**0.018 (0.008,0.028)**	**0.0004**	1.001 (1.000,1.001)	0.0006
PGC & 23andme	$P<10^{-5}$	0.021 (0.001,0.040)	0.038	0.021 (0.000,0.041)	0.046	0.023 (0.004,0.043)	0.019	1.001 (1.000,1.000)	0.078
PGC & 23andme	$P<10^{-6}$	0.027 (-0.006,0.061)	0.109	0.032 (-0.003,0.068)	0.071	0.033 (-0.001,0.066)	0.053	1.003 (1.000,1.010)	0.065
PGC & 23andme	$P<10^{-7}$	0.024 (-0.022,0.070)	0.301	0.032 (-0.016,0.080)	0.190	0.034 (-0.011,0.080)	0.139	1.003 (0.999,1.010)	0.088
PGC & 23andme	$P<10^{-8}$	0.025 (-0.047,0.097)	0.494	0.044 (-0.031,0.120)	0.250	0.033 (-0.039,0.105)	0.362	1.003 (0.997,1.010)	0.379
Okbay	P<0.05	0.005 (0.002,0.008)	0.004	0.005 (0.001,0.008)	0.012	0.004 (0.0007,0.007)	0.018	1.000 (1.000,1.000)	0.019
Okbay	P<0.01	0.004 (-0.0001,0.008)	0.058	0.003 (-0.0006,0.008)	0.093	0.003 (-0.0007,0.0007)	0.104	1.000 (1.000,1.000)	0.079
Okbay	P<0.001	0.003 (-0.003,0.009)	0.348	0.002 (-0.004,0.009)	0.475	0.002 (-0.004,0.008)	0.465	1.000 (1.000,1.000)	0.407
Okbay	$P<10^{-4}$	-0.013 (-0.027,0.001)	0.071	-0.011 (-0.026,0.003)	0.128	-0.009 (-0.023,0.005)	0.215	0.999 (0.998,1.000)	0.121
Okbay	$P<10^{-5}$	-0.001 (-0.031,0.029)	0.939	-0.001 (-0.032,0.030)	0.951	0.004 (-0.026,0.034)	0.785	0.999 (0.997,1.000)	0.494
Okbay	$P<10^{-6}$	0.011 (-0.041,0.062)	0.688	0.005 (-0.049,0.059)	0.848	0.011 (-0.041,0.062)	0.689	0.999 (0.994,1.000)	0.589
Okbay	$P<10^{-7}$	-0.021 (-0.153,0.111)	0.752	-0.018 (-0.157,0.121)	0.800	-0.010 (-0.142,0.122)	0.884	0.998 (0.986,1.010)	0.674
CHARGE	P<0.05	0.001 (-0.002,0.005)	0.400	0.001 (-0.002,0.005)	0.510	0.001 (-0.002,0.005)	0.466	1.000 (1.000,1.000)	0.765
CHARGE	P<0.01	-0.0002 (-0.004,0.004)	0.907	-0.001 (-0.005,0.004)	0.775	-0.001 (-0.005,0.003)	0.663	1.000 (0.999,1.000)	0.364
CHARGE	P<0.001	0.001 (-0.007,0.009)	0.829	0.0002 (-0.008,0.009)	0.963	0.001 (-0.007,0.009)	0.835	1.000 (0.999,1.000)	0.880
CHARGE	$P<10^{-4}$	0.005 (-0.017,0.028)	0.648	0.004 (-0.020,0.028)	0.719	0.001 (-0.022,0.024)	0.943	1.000 (0.998,1.000)	0.955
CHARGE	$P<10^{-5}$	-0.003 (-0.057,0.052)	0.926	-0.017 (-0.074,0.040)	0.557	-0.030 (-0.084,0.025)	0.283	0.999 (0.995,1.000)	0.798

Betas and ORs (95% CI) per unit of the GRSs and p-values were estimated using linear and logistic mixed models (GENESIS and GMMAT) incorporating covariance matrices corresponding to genetic relatedness (kinship), household, and census block group as random effects, and adjusting for center, age, sex, the first five PCs, and sampling weights. Note: The $p<10^{-6}$ and $p<10^{-8}$ GRS were not constructed using the CHARGE and Okbay et al dataset, respectively, due to the small number of SNPs remaining at these thresholds.

Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium Authorship

Naomi R Wray* 1, 2
Stephan Ripke* 3, 4, 5
Manuel Mattheisen* 6, 7, 8, 9
Maciej Trzaskowski* 1
Enda M Byrne 1
Abdel Abdellaoui 10
Mark J Adams 11
Esben Agerbo 9, 12, 13
Tracy M Air 14
Till F M Andlauer 15, 16
Silviu-Alin Bacanu 17
Marie Bækvad-Hansen 9, 18
Aartjan T F Beekman 19
Tim B Bigdeli 17, 20
Elisabeth B Binder 15, 21
Douglas H R Blackwood 11
Julien Bryois 22
Henriette N Buttenschøn 8, 9, 23
Jonas Bybjerg-Grauholm 9, 18
Na Cai 24, 25
Enrique Castelao 26
Jane Hvarregaard Christensen 7, 8, 9
Toni-Kim Clarke 11
Jonathan R I Coleman 27
Lucía Colodro-Conde 28
Baptiste Couvy-Duchesne 29, 30
Nick Craddock 31
Gregory E Crawford 32, 33
Gail Davies 34
Ian J Deary 34
Franziska Degenhardt 35, 36
Eske M Derks 28
Nese Direk 37, 38
Conor V Dolan 10
Erin C Dunn 39, 40, 41
Thalia C Eley 27
Valentina Escott-Price 42
Farnush Farhadi Hassan Kiadeh 43
Hilary K Finucane 44, 45
Andreas J Forstner 35, 36, 46, 47
Josef Frank 48
Héléna A Gaspar 27
Michael Gill 49
Fernando S Goes 50
Scott D Gordon 51
Jakob Grove 7, 8, 9, 52
Lynsey S Hall 11, 53
Christine Søholm Hansen 9, 18
Thomas F Hansen 54, 55, 56
Stefan Herms 35, 36, 47
Ian B Hickie 57
Per Hoffmann 35, 36, 47
Georg Homuth 58
Carsten Horn 59
Jouke-Jan Hottenga 10
David M Hougaard 9, 18
Marcus Ising 60
Rick Jansen 19, 19
Eric Jorgenson 61
James A Knowles 62
Isaac S Kohane 63, 64, 65
Julia Kraft 4
Warren W. Kretzschmar 66
Jesper Krogh 67
Zoltán Kutalik 68, 69
Yihan Li 66
Penelope A Lind 28
Donald J MacIntyre 70, 71
Dean F MacKinnon 50
Robert M Maier 2
Wolfgang Maier 72
Jonathan Marchini 73
Hamdi Mbarek 10
Patrick McGrath 74
Peter McGuffin 27
Sarah E Medland 28
Divya Mehta 2, 75
Christel M Middeldorp 10, 76, 77
Evelin Mihailov 78
Yuri Milaneschi 19, 19
Lili Milani 78
Francis M Mondimore 50
Grant W Montgomery 1
Sara Mostafavi 79, 80
Niamh Mullins 27
Matthias Nauck 81, 82
Bernard Ng 80
Michel G Nivard 10
Dale R Nyholt 83
Paul F O'Reilly 27
Hogni Oskarsson 84
Michael J Owen 85
Jodie N Painter 28
Carsten Bøcker Pedersen 9, 12, 13
Marianne Giørtz Pedersen 9, 12, 13
Roseann E. Peterson 17, 86
Erik Pettersson 22
Wouter J Peyrot 19
Giorgio Pistis 26
Danielle Posthuma 87, 88
Jorge A Quiroz 89
Per Qvist 7, 8, 9
John P Rice 90
Brien P. Riley 17
Margarita Rivera 27, 91
Saira Saeed Mirza 37
Robert Schoevers 92
Eva C Schulte 93, 94
Ling Shen 61
Jianxin Shi 95
Stanley I Shyn 96
Engilbert Sigurdsson 97
Grant C B Sinnamon 98
Johannes H Smit 19
Daniel J Smith 99
Hreinn Stefansson 100
Stacy Steinberg 100
Fabian Streit 48
Jana Strohmaier 48
Katherine E Tansey 101
Henning Teismann 102
Alexander Teumer 103
Wesley Thompson 9, 55, 104, 105

1, Institute for Molecular Bioscience, The University of Queensland, Brisbane, QLD, AU
2, Queensland Brain Institute, The University of Queensland, Brisbane, QLD, AU
3, Analytic and Translational Genetics Unit, Massachusetts General Hospital, Boston, MA, US
4, Department of Psychiatry and Psychotherapy, Universitätsmedizin Berlin Campus Charité Mitte, Berlin, DE
5, Medical and Population Genetics, Broad Institute, Cambridge, MA, US
6, Centre for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, SE
7, Department of Biomedicine, Aarhus University, Aarhus, DK
8, iSEQ, Centre for Integrative Sequencing, Aarhus University, Aarhus, DK
9, iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, DK
10, Dept of Biological Psychology & EMGO+ Institute for Health and Care Research, Vrije Universiteit Amsterdam, Amsterdam, NL
11, Division of Psychiatry, University of Edinburgh, Edinburgh, GB
12, Centre for Integrated Register-based Research, Aarhus University, Aarhus, DK
13, National Centre for Register-Based Research, Aarhus University, Aarhus, DK
14, Discipline of Psychiatry, University of Adelaide, Adelaide, SA, AU
15, Department of Translational Research in Psychiatry, Max Planck Institute of Psychiatry, Munich, DE
16, Munich Cluster for Systems Neurology (SyNergy), Munich, DE
17, Department of Psychiatry, Virginia Commonwealth University, Richmond, VA, US
18, Center for Neonatal Screening, Department for Congenital Disorders, Statens Serum Institut, Copenhagen, DK
19, Department of Psychiatry, Vrije Universiteit Medical Center and GGZ inGeest, Amsterdam, NL
20, Virginia Institute for Psychiatric and Behavior Genetics, Richmond, VA, US
21, Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, US
22, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, SE
23, Department of Clinical Medicine, Translational Neuropsychiatry Unit, Aarhus University, Aarhus, DK
24, Human Genetics, Wellcome Trust Sanger Institute, Cambridge, GB
25, Statistical genomics and systems genetics, European Bioinformatics Institute (EMBL-EBI), Cambridge, GB
26, Department of Psychiatry, University Hospital of Lausanne, Prilly, Vaud, CH
27, MRC Social Genetic and Developmental Psychiatry Centre, King's College London, London, GB
28, Genetics and Computational Biology, QIMR Berghofer Medical Research Institute, Herston, QLD, AU
29, Centre for Advanced Imaging, The University of Queensland, Saint Lucia, QLD, AU
30, Queensland Brain Institute, The University of Queensland, Saint Lucia, QLD, AU
31, Psychological Medicine, Cardiff University, Cardiff, GB
32, Center for Genomic and Computational Biology, Duke University, Durham, NC, US
33, Department of Pediatrics, Division of Medical Genetics, Duke University, Durham, NC, US
34, Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, GB

35, Institute of Human Genetics, University of Bonn, Bonn, DE
36, Life&Brain Center, Department of Genomics, University of Bonn, Bonn, DE
37, Epidemiology, Erasmus MC, Rotterdam, Zuid-Holland, NL
38, Psychiatry, Dokuz Eylul University School Of Medicine, Izmir, TR
39, Department of Psychiatry, Massachusetts General Hospital, Boston, MA, US
40, Psychiatric and Neurodevelopmental Genetics Unit (PNGU), Massachusetts General Hospital, Boston, MA, US
41, Stanley Center for Psychiatric Research, Broad Institute, Cambridge, MA, US
42, Neuroscience and Mental Health, Cardiff University, Cardiff, GB
43, Bioinformatics, University of British Columbia, Vancouver, BC, CA
44, Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, US
45, Department of Mathematics, Massachusetts Institute of Technology, Cambridge, MA, US
46, Department of Psychiatry (UPK), University of Basel, Basel, CH
47, Human Genomics Research Group, Department of Biomedicine, University of Basel, Basel, CH
48, Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Baden-Württemberg, DE
49, Department of Psychiatry, Trinity College Dublin, Dublin, IE
50, Psychiatry & Behavioral Sciences, Johns Hopkins University, Baltimore, MD, US
51, Genetics and Computational Biology, QIMR Berghofer Medical Research Institute, Brisbane, QLD, AU
52, Bioinformatics Research Centre, Aarhus University, Aarhus, DK
53, Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, GB
54, Danish Headache Centre, Department of Neurology, Rigshospitalet, Glostrup, DK
55, Institute of Biological Psychiatry, Mental Health Center Sct. Hans, Mental Health Services Capital Region of Denmark, Copenhagen, DK
56, iPSYCH, The Lundbeck Foundation Initiative for Psychiatric Research, Copenhagen, DK
57, Brain and Mind Centre, University of Sydney, Sydney, NSW, AU
58, Interfaculty Institute for Genetics and Functional Genomics, Department of Functional Genomics, University Medicine and Ernst Moritz Arndt University Greifswald, Greifswald, Mecklenburg-Vorpommern, DE
59, Roche Pharmaceutical Research and Early Development, Pharmaceutical Sciences, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd, Basel, CH
60, Max Planck Institute of Psychiatry, Munich, DE
61, Division of Research, Kaiser Permanente Northern California, Oakland, CA, US
62, Psychiatry & The Behavioral Sciences, University of Southern California, Los Angeles, CA, US
63, Department of Biomedical Informatics, Harvard Medical School, Boston, MA, US
64, Department of Medicine, Brigham and Women's Hospital, Boston, MA, US
65, Informatics Program, Boston Children's Hospital, Boston, MA, US
66, Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, GB
67, Department of Endocrinology at Herlev University Hospital, University of Copenhagen, Copenhagen, DK
68, Institute of Social and Preventive Medicine (IUMSP), University Hospital of Lausanne, Lausanne, VD, CH

69, Swiss Institute of Bioinformatics, Lausanne, VD, CH
70, Division of Psychiatry, Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, GB
71, Mental Health, NHS 24, Glasgow, GB
72, Department of Psychiatry and Psychotherapy, University of Bonn, Bonn, DE
73, Statistics, University of Oxford, Oxford, GB
74, Psychiatry, Columbia University College of Physicians and Surgeons, New York, NY, US
75, School of Psychology and Counseling, Queensland University of Technology, Brisbane, QLD, AU
76, Child and Youth Mental Health Service, Children's Health Queensland Hospital and Health Service, South Brisbane, QLD, AU
77, Child Health Research Centre, University of Queensland, Brisbane, QLD, AU
78, Estonian Genome Center, University of Tartu, Tartu, EE
79, Medical Genetics, University of British Columbia, Vancouver, BC, CA
80, Statistics, University of British Columbia, Vancouver, BC, CA
81, DZHK (German Centre for Cardiovascular Research), Partner Site Greifswald, University Medicine, University Medicine Greifswald, Greifswald, Mecklenburg-Vorpommern, DE
82, Institute of Clinical Chemistry and Laboratory Medicine, University Medicine Greifswald, Greifswald, Mecklenburg-Vorpommern, DE
83, Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, QLD, AU
84, Humus, Reykjavik, IS
85, MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff, GB
86, Virginia Institute for Psychiatric & Behavioral Genetics, Virginia Commonwealth University, Richmond, VA, US
87, Clinical Genetics, Vrije Universiteit Medical Center, Amsterdam, NL
88, Complex Trait Genetics, Vrije Universiteit Amsterdam, Amsterdam, NL
89, Solid Biosciences, Boston, MA, US
90, Department of Psychiatry, Washington University in Saint Louis School of Medicine, Saint Louis, MO, US
91, Department of Biochemistry and Molecular Biology II, Institute of Neurosciences, Center for Biomedical Research, University of Granada, Granada, ES
92, Department of Psychiatry, University of Groningen, University Medical Center Groningen, Groningen, NL
93, Department of Psychiatry and Psychotherapy, Medical Center of the University of Munich, Campus Innenstadt, Munich, DE
94, Institute of Psychiatric Phenomics and Genomics (IPPG), Medical Center of the University of Munich, Campus Innenstadt, Munich, DE
95, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, US
96, Behavioral Health Services, Kaiser Permanente Washington, Seattle, WA, US
97, Faculty of Medicine, Department of Psychiatry, University of Iceland, Reykjavik, IS
98, School of Medicine and Dentistry, James Cook University, Townsville, QLD, AU
99, Institute of Health and Wellbeing, University of Glasgow, Glasgow, GB
100, deCODE Genetics / Amgen, Reykjavik, IS
101, College of Biomedical and Life Sciences, Cardiff University, Cardiff, GB

102, Institute of Epidemiology and Social Medicine, University of Münster, Münster, Nordrhein-Westfalen, DE
103, Institute for Community Medicine, University Medicine Greifswald, Greifswald, Mecklenburg-Vorpommern, DE
104, Department of Psychiatry, University of California, San Diego, San Diego, CA, US
105, KG Jebsen Centre for Psychosis Research, Norway Division of Mental Health and Addiction, Oslo University Hospital, Oslo, NO
106, Medical Genetics Section, CGEM, IGMM, University of Edinburgh, Edinburgh, GB
107, Clinical Neurosciences, University of Cambridge, Cambridge, GB
108, Internal Medicine, Erasmus MC, Rotterdam, Zuid-Holland, NL
109, Roche Pharmaceutical Research and Early Development, Neuroscience, Ophthalmology and Rare Diseases Discovery & Translational Medicine Area, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd, Basel, CH
110, Department of Psychiatry and Psychotherapy, University Medicine Greifswald, Greifswald, Mecklenburg-Vorpommern, DE
111, Department of Psychiatry, Leiden University Medical Center, Leiden, NL
112, Virginia Institute of Psychiatric & Behavioral Genetics, Virginia Commonwealth University, Richmond, VA, US
113, Computational Sciences Center of Emphasis, Pfizer Global Research and Development, Cambridge, MA, US
114, Institute for Molecular Bioscience; Queensland Brain Institute, The University of Queensland, Brisbane, QLD, AU
115, Department of Psychiatry, University of Münster, Münster, Nordrhein-Westfalen, DE
116, Institute of Medical Genetics and Pathology, University Hospital Basel, University of Basel, Basel, CH
117, Institute of Neuroscience and Medicine (INM-1), Research Center Juelich, Juelich, DE
118, Amsterdam Public Health Institute, Vrije Universiteit Medical Center, Amsterdam, NL
119, Centre for Integrative Biology, Università degli Studi di Trento, Trento, Trentino-Alto Adige, IT
120, Department of Psychiatry and Psychotherapy, Medical Center, University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, DE
121, Psychiatry, Kaiser Permanente Northern California, San Francisco, CA, US
122, Medical Research Council Human Genetics Unit, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, GB
123, Department of Psychiatry, University of Toronto, Toronto, ON, CA
124, Centre for Addiction and Mental Health, Toronto, ON, CA
125, Division of Psychiatry, University College London, London, GB
126, Neuroscience Therapeutic Area, Janssen Research and Development, LLC, Titusville, NJ, US
127, Institute of Molecular and Cell Biology, University of Tartu, Tartu, EE
128, Psychosis Research Unit, Aarhus University Hospital, Risskov, Aarhus, DK
129, University of Liverpool, Liverpool, GB
130, Mental Health Center Copenhagen, Copenhagen University Hospital, Copenhagen, DK
131, Human Genetics and Computational Biomedicine, Pfizer Global Research and Development, Groton, CT, US
132, Psychiatry, Harvard Medical School, Boston, MA, US

133, Psychiatry, University of Iowa, Iowa City, IA, US
134, Department of Psychiatry and Behavioral Sciences, Johns Hopkins University, Baltimore, MD, US
135, Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Goettingen, Niedersachsen, DE
136, Human Genetics Branch, NIMH Division of Intramural Research Programs, Bethesda, MD, US
137, Faculty of Medicine, University of Iceland, Reykjavik, IS
138, Child and Adolescent Psychiatry, Erasmus MC, Rotterdam, Zuid-Holland, NL
139, Psychiatry, Erasmus MC, Rotterdam, Zuid-Holland, NL
140, Psychiatry, Dalhousie University, Halifax, NS, CA
141, Division of Epidemiology, New York State Psychiatric Institute, New York, NY, US
142, Department of Clinical Medicine, University of Copenhagen, Copenhagen, DK
143, Department of Medical & Molecular Genetics, King's College London, London, GB
144, Psychiatry & Behavioral Sciences, Stanford University, Stanford, CA, US
145, NIHR BRC for Mental Health, King's College London, London, GB
146, Genetics, University of North Carolina at Chapel Hill, Chapel Hill, NC, US
147, Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, NC, US

References

1. Sorlie PD, Aviles-Santa LM, Wassertheil-Smoller S, et al. Design and implementation of the Hispanic Community Health Study/Study of Latinos. *Ann Epidemiol* 2010;20(8):629-41. doi: 10.1016/j.annepidem.2010.03.015
2. Lavange LM, Kalsbeek WD, Sorlie PD, et al. Sample design and cohort selection in the Hispanic Community Health Study/Study of Latinos. *Annals of Epidemiology* 2010;20(8):642-9. doi: 10.1016/j.annepidem.2010.05.006
3. Laurie CC, Doheny KF, Mirel DB, et al. Quality control and quality assurance in genotypic data for genome-wide association studies. *Genet Epidemiol* 2010;34(6):591-602. doi: 10.1002/gepi.20516
4. Laurie CC, Laurie CA, Rice K, et al. Detectable clonal mosaicism from birth to old age and its relationship to cancer. *Nat Genet* 2012;44(6):642-50. doi: 10.1038/ng.2271
5. Genomes Project C, Abecasis GR, Auton A, et al. An integrated map of genetic variation from 1,092 human genomes. *Nature* 2012;491(7422):56-65. doi: 10.1038/nature11632
6. Howie BN, Donnelly P, Marchini J. A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. *PLoS Genet* 2009;5(6):e1000529. doi: 10.1371/journal.pgen.1000529
7. Howie BN, Marchini J, Stephens M. Genotype imputation with thousands of genomes. *G3: Genes, Genomics, Genetics* 2011;1:457-70.
8. Manichaikul A, Mychaleckyj JC, Rich SS, et al. Robust relationship inference in genome-wide association studies. *Bioinformatics* 2010;26(22):2867-73. doi: 10.1093/bioinformatics/btq559
9. Thornton T, Tang H, Hoffmann TJ, et al. Estimating kinship in admixed populations. *Am J Hum Genet* 2012;91(1):122-38. doi: 10.1016/j.ajhg.2012.05.024
10. Conomos MP, Miller MB, Thorton TA. Robust inference of population structure for ancestry prediction and correction of stratification in the presence of relatedness. *Genetic Epidemiology* 2015
11. Hek K, Demirkan A, Lahti J, et al. A genome-wide association study of depressive symptoms. *Biological Psychiatry* 2013;73(7):667-78. doi: 10.1016/j.biopsych.2012.09.033 [published Online First: 2013/01/08]
12. Levy D, DeStefano AL, Larson MG, et al. Evidence for a gene influencing blood pressure on chromosome 17: Genome scan linkage results for longitudinal blood pressure phenotypes in subjects from the Framingham Heart Study. *Hypertension* 2000;36(4):477-83.
13. Design of the Women's Health Initiative clinical trial and observational study. The Women's Health Initiative Study Group. *Control and Clinical Trials* 1998;19:61-109.
14. Wassertheil-Smoller S, Shumaker S, Ockene J, et al. Depression and cardiovascular sequela in postmenopausal women: The Women's Health Initiative (WHI). *Archives of Internal Medicine* 2004;164:289-98.
15. Women's Health Initiative SHARe Project. Imputation Report - 1000 Genomes Project reference panel 2011 [Available from: https://www.garnetstudy.org/sites/www/content/files/dataflowcleaning/WHI_SHARe_qc_report_1000G_final.pdf.
16. Browning B, Browning SA. A unified approach to genotype imputation and haplotype-phase inference for large data sets of trios and unrelated individuals. *American Journal of Human Genetics* 2009;84:210-23.

17. Price AL, Patterson NJ, Plenge RM, et al. Principal components analysis corrects for stratification in genome-wide association studies. *Nature Genetics* 2006;38:904-09.
18. Bild DE, Bluemke DA, Burke GL, et al. Multi-ethnic study of atherosclerosis: objectives and design. *Am J Epidemiol* 2002;156(9):871-81.
19. Ursano RJ, Colpe LJ, Heeringa SG, et al. The Army study to assess risk and resilience in servicemembers (Army STARRS). *Psychiatry* 2014;77(2):107-19. doi: 10.1521/psyc.2014.77.2.107
20. Ripke S, O'Dushlaine C, Chambert K, et al. Genome-wide association analysis identifies 13 new risk loci for schizophrenia. *Nat Genet* 2013;45(10):1150-9. doi: 10.1038/ng.2742
21. Delaneau O, Marchini J, Zagury JF. A linear complexity phasing method for thousands of genomes. *Nat Methods* 2012;9(2):179-81. doi: 10.1038/nmeth.1785
22. Howie B, Marchini J, Stephens M. Genotype imputation with thousands of genomes. *G3 (Bethesda)* 2011;1(6):457-70. doi: 10.1534/g3.111.001198
23. Wassertheil-Smoller S, Shumaker S, Ockene J, et al. Depression and cardiovascular sequelae in postmenopausal women. The Women's Health Initiative (WHI). *Arch Intern Med* 2004;164(3):289-98. doi: 10.1001/archinte.164.3.289
24. Borhani NO, Applegate WB, Cutler JA, et al. Systolic Hypertension in the Elderly Program (SHEP). Part 1: Rationale and design. *Hypertension* 1991;17(3 Suppl):II2-15.
25. Radloff LF. The CES-D scale: a self-report depression scale for research in the general public. *Appl Psychol Meas* 1977;1:385–401.
26. Kessler RC, Calabrese JR, Farley PA, et al. Composite International Diagnostic Interview screening scales for DSM-IV anxiety and mood disorders. *Psychol Med* 2013;43(8):1625-37. doi: 10.1017/S0033291712002334