DEPRESSION AND ANXIETY 33:265–280 (2016)

2015 Donald F Klein Investigator Award Winner

GENOME-WIDE ASSOCIATION STUDY (GWAS) AND GENOME-WIDE BY ENVIRONMENT INTERACTION STUDY (GWEIS) OF DEPRESSIVE SYMPTOMS IN AFRICAN AMERICAN AND HISPANIC/LATINA WOMEN

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Financial Disclosures: All authors report no biomedical financial interests or potential conflicts of interest.

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Contract grant sponsor: National Institute of Mental Health of the National Institutes of Health; Contract grant numbers: K01MH102403 and K24MH094614; Contract grant sponsor: NARSAD Young Investigator Grant from the Brain & Behavior Research Foundation. Contract grant sponsor: the National Heart, Lung, and Blood Institute; Contract grant sponsor: U.S. Department of Health and Human Services; Contract grant numbers: HHSN268201100046C, HHSN268201100001C, HHSN 268201100002C, HHSN268201100003C, HHSN268201100004C, and HHSN271201100004C. Contract grant sponsor: National Institute on Aging; Contract grant number: NIA U01AG009740, RC2 AG036495, and RC4 AG039029.

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Received for publication 31 July 2015; Revised 12 February 2016; Accepted 12 February 2016

DOI 10.1002/da.22484
Published online in Wiley Online Library (wileyonlinelibrary.com).

Background: *Genome-wide association studies (GWAS) have made little progress in identifying variants linked to depression. We hypothesized that examining depressive symptoms and considering gene–environment interaction (GxE) might improve efficiency for gene discovery. We therefore conducted a GWAS and genome-wide by environment interaction study (GWEIS) of depressive symptoms.* **Methods:** *Using data from the SHARe cohort of the Women's Health Initiative, comprising African Americans (n = 7,179) and Hispanics/Latinas (n = 3,138), we examined genetic main effects and GxE with stressful life events and social support. We also conducted a heritability analysis using genome-wide complex trait analysis (GCTA). Replication was attempted in four independent cohorts.* **Results:** *No SNPs achieved genome-wide significance for main effects in either discovery sample. The top signals in African Americans were rs73531535 (located 20 kb from GPR139, $P = 5.75 \times 10^{-8}$) and rs75407252 (intronic to CACNA2D3, $P = 6.99 \times 10^{-7}$). In Hispanics/Latinas, the top signals were rs2532087 (located 27 kb from CD38, $P = 2.44 \times 10^{-7}$) and rs4542757 (intronic to DCC, $P = 7.31 \times 10^{-7}$). In the GEWIS with stressful life events, one interaction signal was genome-wide significant in African Americans (rs4652467; $P = 4.10 \times 10^{-10}$; located 14 kb from CEP350). This interaction was not observed in a smaller replication cohort. Although heritability estimates for depressive symptoms and stressful life events were each less than 10%, they were strongly genetically correlated (rG = 0.95), suggesting that common variation underlying self-reported depressive symptoms and stressful life event exposure, though modest on their own, were highly overlapping in this sample.* **Conclusions:** *Our results underscore the need for larger samples, more GEWIS, and greater investigation into genetic and environmental determinants of depressive symptoms in minorities. Depression and Anxiety 33:265–280, 2016.*

Key words: *genome-wide association study; gene-environment interaction; depression; stressful life events; social support*

INTRODUCTION

Although family and twin studies show that depression is driven partly by genetic variation,[1] until just recently,[2] genome-wide association studies (GWAS) have made little progress in identifying specific loci linked to depression.[3] Several factors could explain the lack of success, including the complex genetic architecture of depression, small samples, and heterogeneity in the "depression" phenotype.[4,5] Moreover, with the exception of two studies,[6,7] including a large meta-analysis,[6] most prior GWAS have examined diagnoses, rather than quantitative traits (e.g., depressive symptoms). In light of evidence suggesting the diagnostic categories have been artificially imposed on a continuum of depression risk,[8] such case-control analyses may have limitations. For example, simulations studies demonstrate that for common phenotypes (i.e., with prevalence greater than 10%), the quantitative trait approach may have power advantages under certain conditions in population-based samples.[9] GWAS have also neglected the role of gene-environment interaction (GxE),[10] which many believe contributes to the etiology of depression.[11,12] Previous GxE studies have been limited to candidate genes; these results have been highly controversial.[13–16] Studies of GxE in the context of GWAS for psychiatric phenotypes are needed and may be informative for identifying novel genomic loci.[17,18] Indeed, GxE studies using genome-wide data for other complex phenotypes have revealed genotype–phenotype associations not apparent in genetic main effect analyses.[19–21]

Further, genetic studies of depression and other psychiatric phenotypes have almost exclusively comprised samples of European ancestry, leaving racial/ethnic minorities underrepresented in psychiatric genetics research. Extending genetic association studies to more diverse racial/ethnic populations—especially of women—is therefore needed. These studies are likely to be informative, as depression appears at least as heritable (around 40%) among African Americans[22,23] and Hispanics [24] compared to European Americans.[1] Such extensions are also important given known racial/ethnic (as well as sex) disparities. For example, epidemiological studies have observed lower lifetime prevalence estimates for major depressive disorder (MDD) among non-Whites,[25] despite a higher burden of social-environmental adversity from stressful life events,[26]

discrimination,[27,28] and lower socioeconomic status.[29] Epidemiological studies have also consistently showed a twofold elevated risk of MDD in women compared to men.[30]

Here, we aimed to address these limitations by conducting a GWAS of depressive symptoms and performing a genome-wide by environment interaction study (GWEIS), sometimes referred to as genomewide interaction scans, using data from a large population-based epidemiological sample of African American and Hispanic/Latina women drawn from the Women's Health Initiative (WHI).

METHODS AND MATERIALS

OVERVIEW

As described elsewhere[31,32] (www.whi.org), the WHI consists of an observational study (WHI-OS) and randomized clinical trial (WHI-CT). The WHI-OS prospectively followed 93,676 postmenopausal women ages 50–79 recruited from 40 clinical centers in the United States between 1993 and 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 supplementation. We analyzed data from women genotyped as part of the WHI SNP Health Association Resource (SHARe), a sub-study of self-reported minority women in WHI ($n = 7{,}480$ African American and 3,352 Hispanic/Latina women). All participants consented to be included in studies for general research use. Data were downloaded from the database of Genotypes and Phenotypes (dbGaP; accession #phs000200.v9.p3).

PHENOTYPE DEFINITION

Depressive symptoms were assessed at enrollment using total scores from a six-item version of the Center for Epidemiological Studies of Depression Scale (CES-D),[33] a widely-used measure of depressive symptoms in epidemiological studies. The six-item CES-D captured core symptoms of depression in the past week, including anhedonia, depressed mood, and behavioral symptoms (e.g., felt depressed; sleep was restless; enjoyed life; had crying spells; felt sad; felt people disliked you). The six-item scale correlates highly with the full 20-item CES-D ($r = 0.88$).[32] Brief versions of the CES-D correlate highly in older adults with diagnoses of MDD obtained from structured interviews.[34]

As CES-D scores in this population-based sample could have been influenced by antidepressant medication use, we used a nonparametric imputation algorithm developed in a previous GWAS of depressive symptoms[6] to adjust the CES-D score of women taking antidepressants (as determined by pill bottles women brought to the baseline interview). This algorithm, which increased the CES-D score for all antidepressant users, was based on one used to adjust blood pressure for persons on antihypertensive medications[35] (see Supporting Information).

We tested for statistical GxE interaction with two environmental exposures—stressful life events and social support—both of which were shown to correlate with depressive symptoms in WHI[32] and numerous other studies.[36] These two social–environmental exposures were measured at enrollment, concurrently with depressive symptoms. Stressful life events were assessed using a scale modified from the Almeida County Study,[37,38] which asked women to indicate whether they had experienced 11 different major losses or traumatic events in the past year (see Supporting Information for specific items). Items were summed to create a total count of the number of past-year stressors among those with complete data on all stressors (ranging from 0 to 11). Social support was assessed using nine items from the 19-item Medical Outcome Survey.[39] We summed across these items to obtain a measure for level of perceived social support.

SNP GENOTYPING AND IMPUTATION

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 720,101 (African Americans) and 709,042 (Hispanics/Latinas) SNPs passed preimputation filters.

Quality control procedures were performed at the Fred Hutchinson Cancer Research Center (FHCRC) in Seattle, WA. As described elsewhere (refer to[40] and Supporting Information), the WHI GARNET Coordinating Center (www.garnetstudy.org) performed the imputation using the 1000 Genomes Interim reference panel (release December 2010) and BEAGLE software version 3.3.1.[41]

QUALITY CONTROL (QC) OF SNPS AND SAMPLES

In addition to the QC standards imposed by WHI, we additionally excluded SNPs with a MAF of ≤2% or imputation quality score $< r^2 = 0.80$. Population stratification was assessed by WHI investigators using a principal components analysis estimated by the program EIGENSTRAT.[42] A total of 61 genetic outliers were removed from the African American analysis based on their PCA scores. After QC, 10,771 women (7,419 African American and 3,352 Hispanic/Latina women) were available for analysis. Allele dosages (meaning the probability of the three possible genotypes), rather than hard-called or "best guess" genotypes, were used for both the GWAS and GWEIS analyses.

STATISTICAL ANALYSES

GWAS Analysis. We performed a GWAS, using PLINK version 1.07,[43] separately for African Americans and Hispanics/Latinas. We used linear regression for all analyses, modeled each SNP additively, and used the standard 5×10^{-8} as our threshold for statistical significance. After obtaining GWAS results, SNPs were clumped according to linkage disequilibrium (LD) to identify independent loci represented by a single best SNP.[43] This clump procedure used the following thresholds to identify independent SNPs: (1) SNPs that had LD $r^2 \geq 0.25$; and (2) SNPs that were within 250 kb. We also analyzed SNPs on the X chromosome.

Both GWAS analyses (and the GWEIS, described below) adjusted for the following covariates, measured at baseline: age, income, education, marital status, and four principal components adjusting for population structure.[40] These covariates were included because each was associated with depressive symptoms in either the SHARe or larger WHI cohort,[32] and prior studies have suggested inclusion of covariates in GWAS of common phenotypes may increase power.[44] Quantile-quantile (QQ) and Manhattan plots were generated using R.[45] Regional association plots were generated using Locus Zoom.[46] Inverse variance weighted fixed-effect meta-analyses were conducted using METAL (http://www.sph.umich.edu/csg/abecasis/metal/;[47]).

GWEIS Analysis. We performed the GWEIS using probABEL.[48] Both stressful life events and social support were modeled separately using a categorical variable derived by taking quartiles of the total score distribution (0 = first quartile; 1 = second quartile; 2 = third quartile; 3 = fourth quartile). The lowest quartile group (0) indicated the lowest social-environmental risk group, whereas the highest quartile group (3) indicated the highest social-environmental risk group. We used quartiles to facilitate interpretation and address the skewed distribution of these variables; categorization (into four or more categories) does not result in the loss of information (and power) that occurs when continuous variables are dichotomized.[49] We tested for GxE by including dummy variables

for quartile group as well as a SNP by quartile-group (treated as ordinal) interaction term in the model. We used a Bonferroni correction to establish a significance threshold accounting for multiple testing of two environmental exposures ($\alpha = 2.5 \times 10^{-8}$). To reduce the likelihood of spurious GxE findings, we used model-robust estimates of standard errors (also known as sandwich standard errors)[50] in all tests of GxE. Robust variance estimates can reduce the possibility of inflated Type I errors found for GxE effects if the environmental main effect is misspecified or if there is departure from the presumed linear model.[51–53] *P*-values corresponding to the interaction term (in the multiple regression model) were calculated in R based on a Wald chi-square test.

REPLICATION

We sought replication of top GWAS findings ($P < 1 \times 10^{-6}$) in each sample using data from four independent cohorts (see Supporting Information); two cohorts (HRS and HCHS/SOL) were also used to replicate the GWEIS results. For the African American replication, we analyzed data from African American women in the Health and Retirement Study (HRS; $n = 1{,}231$; mean age 62.09),[54,55] where depressive symptoms were measured using an 8-item version of the CES-D, social support was measured through three items asking about support received from a spouse, children, family, and friends, and stressful life events were measured through a composite measure developed to most closely approximate the discovery analysis. We also analyzed data from African Americans in the Grady Trauma Project (GTP; $n = 2{,}010$ women ages 18–65),[56] where depressive symptoms were assessed using the Beck Depression Inventory.[57] For the Hispanic/Latino replication, we analyzed data from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL; $n = 3{,}371$ women ages 50–76), where depressive symptoms were measured by a 10-item CES-D, social support was measured through the 12-item version of the Interpersonal Support Evaluation List,[58] and stressful life events was assessed through a composite measure designed to match the discovery sample. We also assessed top GWAS findings for both Hispanics and African Americans in the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE Consortium), which performed the largest meta-analysis GWAS of depressive symptoms to date using 17 European-ancestry population-based studies ($n = 51{,}258$ individuals) of older adults where depressive symptoms were measured through the CES-D.[6]

SECONDARY ANALYSES

We performed four secondary analyses. First, we conducted two sets of meta analyses to determine the degree to which the top GWAS SNPs ($P < 10^{-5}$) obtained in African Americans also showed evidence of nominal association in Hispanics/Latinas and vice versa. Second, we reran the GWAS in each sample after additionally adjusting for both environmental exposures, as both stressful life events and social support were found to make large and unique contributions to the variance in depressive symptoms. Third, we performed an analysis using genome-wide complex trait analysis (GCTA), which uses restricted maximum likelihood (REML) to obtain an estimation of the additive effect of common variants or "SNP-chip heritability."[59] We conducted these analyses, focusing on depressive symptoms, stressful life events, and social support separately, to evaluate the unique genetic contribution to these phenotypes and the potential presence of gene–environment correlation. We also examined the genetic contribution to depressive symptoms after adjusting for each of these environmental exposures individually. These analyses were performed only in African Americans, as a power calculation indicated the Hispanic/Latino sample would be underpowered to detect SNP heritability estimates in the range reported in previous studies of European Americans (ranging from 21[60] to 32%[61] for major depressive disorder; MDD). We also performed a bivariate REML analysis to determine the genetic correlation between depressive symptoms and these two environmental exposures.[62] Finally, to evaluate the strength of our findings given the skewed distribution of our outcome, we repeated the top GWAS ($P < 1 \times 10^{-5}$) and GWEIS ($P < 1 \times 10^{-6}$) tests of association using a nonparametric bootstrap. For the top GWAS SNPs, we fit a linear regression on 1,000 bootstrap samples using the boot package in R[63,64] and compared the effective sizes (betas) from the bootstrap samples to the betas obtained in the original analysis for each top SNP. For the top GWEIS SNPs, we fit linear regressions to 5,000 datasets simulated under the null hypothesis[65] and generated *P*-values for each top SNP. These *P*-values represent the number of betas that were more extreme than the beta obtained in the original analysis divided by 5,000 replicates. A significant *P*-value therefore indicates that the GxE interaction is significant at that level.

RESULTS

DISCOVERY SAMPLE: GWAS

There were 7,179 African American and 3,138 Hispanic/Latina women in the analysis. See Supporting Information Table S1 for sample demographic characteristics. Depressive symptoms scores were slightly higher in Hispanics/Latinas (mean = 3.27; sd = 3.20) and skewed toward lower values (skew = 1.22; kurtosis = 1.24), particularly in African Americans (mean = 2.52; sd = 2.71; skew = 1.55; kurtosis = 2.97). However, as linear regression is robust to minor violations of normality[66] and tests of GxE are sensitive to changing the scale of the phenotype,[67] we did not perform any transformations.

Manhattan and QQ plots are shown in Supporting Information Fig. S1. As shown in the QQ plot, there was no evidence of inflation in either the African American ($\lambda = 1.004$, median = 0.458) or Hispanic/Latina ($\lambda = 0.998$, median = 0.455) GWAS.

No SNPs achieved genome-wide significance in either sample (Table 1). The peak signal in African Americans ($P = 5.75 \times 10^{-8}$) was for an imputed SNP rs73531535 located 20 kb from *GPR139* (the G protein coupled receptor 139), although several other SNPs in the region that also showed support were genotyped (Supporting Information Fig. S2). The second strongest association signal in African Americans was observed at rs75407252 ($P = 6.99 \times 10^{-7}$), in an intron of *CACNA2D3*, which encodes a voltage-dependent calcium channel subunit (Supporting Information Fig. S3).

In Hispanics/Latinas, the peak signal ($P = 2.44 \times 10^{-7}$) was for an imputed SNP rs2532087 located approximately 27 kb away from *CD38* (Supporting Information Fig. S4). The second strongest association signal was for the imputed SNP rs4542757 ($P = 7.31 \times 10^{-7}$) located in an intron of *DCC* (deleted in colorectal cancer; Supporting Information Fig. S5). All GWAS results at $P < 1 \times 10^{-4}$ are shown for African Americans (Supporting Information Table S2) and Hispanics/Latinas (Supporting Information Table S3). No SNPs achieved genome-wide significance on the X chromosome for either sample (Supporting Information Table S4).

TABLE 1. Genome-wide association study (GWAS) results for the top loci ($p<1\times10^{-5}$) in African Americans and Hispanics/Latinos

SNP	chr	position	A1	A2	MAF	G/I	Info	Beta	SE	P-value	Location	Closest Gene (<20kb)
African Americans												
rs73531535	16	20105038	C	T	0.229	I	0.938	-0.297	0.055	5.75E-08		*GPR139*
rs75407252	3	54241886	C	T	0.053	I	0.813	-0.548	0.110	6.99E-07	intron variant	*CACNA2D3*
rs11233283	11	82415904	A	G	0.016	I	0.986	-0.298	0.062	1.41E-06		
rs34257140	17	42675053	G	T	0.149	I	0.999	-0.313	0.065	1.59E-06		
rs580112	3	177289895	A	G	0.184	I	0.945	0.279	0.060	2.84E-06	intron variant	*LINC00578*
rs1413154	13	83240729	G	T	0.205	I	0.825	-0.283	0.061	3.54E-06		
rs1893586	21	43286918	A	G	0.483	I	0.947	0.211	0.046	4.19E-06	intron variant	*PRDM15*
rs10777901	12	98492992	A	C	0.481	I	0.993	0.206	0.045	4.27E-06		
rs10125319	9	133426729	C	T	0.491	I	0.920	-0.214	0.047	4.27E-06		
rs10221121	16	56840328	A	G	0.229	G	0.986	-0.241	0.053	5.98E-06	intron variant	*NUP93*
rs210329	14	54059800	G	T	0.332	I	0.989	0.217	0.048	6.35E-06		*RPS3AP46*
rs28493952	3	95747804	C	T	0.320	I	0.850	0.234	0.052	6.41E-06		
rs7312307	12	106441333	C	G	0.087	I	0.904	0.376	0.084	6.92E-06		*NUAK1*
rs17030391	2	43353504	A	G	0.143	I	0.808	0.316	0.071	7.84E-06		
rs4866976	5	45579793	A	G	0.086	G	0.996	-0.361	0.081	8.04E-06	intron variant	*HCN1*
rs418207	3	9225376	A	G	0.477	I	0.811	-0.219	0.050	9.59E-06	intron variant	*SRGAP3*
Hispanics/Latinos												
rs2532087	4	15878327	C	G	0.231	I	0.8154	0.5379	0.104	2.44E-07		
rs4542757	18	50198724	C	T	0.418	I	0.9304	-0.4135	0.0833	7.31E-07	intron variant	*DCC*
rs10249677	7	50650831	G	T	0.042	I	0.8816	1.0497	0.2157	1.20E-06		*GRB10*
rs1129411	2	231077725	A	G	0.085	I	0.9941	0.6637	0.1417	2.94E-06	missense/intron variant	*SP110*
rs11738766	5	8214282	A	G	0.279	G	1.0253	-0.4134	0.0885	3.11E-06		
rs34359572	1	194036781	A	G	0.072	I	0.8899	-0.7471	0.1619	4.10E-06		
rs609508	20	54167720	C	G	0.214	I	0.9752	0.4429	0.097	5.21E-06		
rs16823787	2	183692791	A	G	0.084	G	0.9823	0.6591	0.1444	5.21E-06		*FRZB*
rs17345417	4	95948486	A	G	0.111	G	0.9949	-0.574	0.1259	5.30E-06	intron variant	*BMPR1B*
rs2822657	21	15774729	C	T	0.457	I	0.9875	-0.3657	0.0802	5.35E-06		*HSPA13*
rs13033587	2	52857818	C	T	0.475	I	0.9342	0.376	0.0828	5.85E-06		
rs9601962	13	83312889	G	T	0.185	I	0.8544	0.4945	0.1098	6.91E-06		
rs2282123	6	89907561	C	G	0.255	G	1.0034	0.4114	0.0915	7.19E-06	intron variant	*GABRR1*
rs10886733	10	122402887	C	T	0.117	I	0.9766	0.556	0.1237	7.23E-06		*MIR5694*
rs61848143	10	24746704	C	G	0.177	I	0.8403	-0.5023	0.1122	7.85E-06	intron variant	*KIAA1217*
rs10166852	2	183450923	C	G	0.474	I	0.9666	-0.3752	0.0838	7.85E-06		
rs6736484	2	45146524	G	T	0.075	G	0.8556	-0.7206	0.1621	9.05E-06		
rs2912513	8	69968166	A	T	0.033	I	0.9774	-0.996	0.2243	9.33E-06	intron variant	*LINC01592*

The table lists all LD-pruned SNPs associated with depressive symptoms at $p<1\times10^{-5}$. A1 is the tested allele using an additive model, where allele dosages were analyzed. The closest gene within 20kb upstream/downstream of the SNP is provided. All SNPs are on the positive (5′ to 3′) strand. Chr: chromosome; position: base pair position, G/I: genotyped or imputed.

REPLICATION SAMPLES: GWAS

Sixteen SNPs from the African American analysis and 18 SNPs from the Hispanic/Latina analysis with $P < 1 \times 10^{-5}$ were evaluated in four independent samples. For the African American replication (Table 2), one SNP was nominally significant in the HRS (rs418207; $P = 0.015$), though was not statistically associated after correction for multiple testing ($\alpha = 0.003$). This SNP showed the same direction and magnitude of effect in WHI and HRS and is intronic to *SRGAP3*, the gene that encodes the enzyme SLIT-ROBO Rho GTPase-activating 3.

In the Hispanic/Latina replication (Table 3), the peak WHI signal (rs2532087) also had the lowest *P*-value of the 18 SNPs in HCHS/SOL ($P = 0.00964$), though this result was not significantly associated after multiple testing correction ($\alpha = 0.003$). However, the direction and effect size were nearly identical in both the discovery and replication samples (WHI $\beta = 0.54$; HCHS/SOL $\beta = 0.56$). The Hispanic/Latina discovery and HCHS/SOL replication results were also highly concordant, with 72% of linear regression β coefficients (13 out of 18 SNPs) yielding the same direction of effect (sign test $P = 0.05$). None of the top GWAS findings in African Americans or Hispanics/Latinas were significantly associated with depressive symptoms in the CHARGE consortium of European Americans (refer to Supporting Information Table S5).

DISCOVERY SAMPLE: GWEIS

Women in each sample reported a similar number of stressful life events (African American mean = 2.15, sd = 1.57; Hispanic/Latina mean = 2.13, sd = 1.68) and levels of social support (African American mean = 35.29, sd = 7.63; Hispanic/Latina mean = 34.27, sd = 8.92). The number of stressful life events and depressive symptoms were *positively* associated in both African Americans ($r^2 = 0.10$; $P < 0.001$) and Hispanics/Latinas ($r^2 = 0.10$; $P < 0.001$). Social support was *negatively* associated with depressive symptoms in both African Americans ($r^2 = 0.09$; $P < 0.001$) and Hispanics/Latinas ($r^2 = 0.15$; $P < 0.001$).

There was no evidence of genomic inflation for the African American stressful life events ($\lambda = 0.99$) and social support analyses ($\lambda = 1.02$) or the Hispanic/Latina stressful life events ($\lambda = 1.01$) and social support analyses ($\lambda = 1.03$) (Supporting Information Figs. S6 and S7).

One association signal was genome-wide significant (rs4652467; $P = 4.10 \times 10^{-10}$) in African Americans for the stressful life events GWEIS (Table 4). This SNP, located within 20 kb of *CEP350*, was imputed, as were other SNPs in the region with $P < 2.4 \times 10^{-8}$ (Fig. 1). The second strongest signal in African Americans was rs7275997 ($P = 1.22 \times 10^{-7}$), a genotyped intronic SNP located in *TMPRSS15* (transmembrane protease, serine 15; Supporting Information Fig. S8). The GWEIS of social support in African Americans did not yield any genome-wide significant results (Table 4). The top two loci were rs77966298 ($P = 2.43 \times 10^{-7}$; Supporting Information Fig. S9) and rs6419121 ($P = 3.98 \times 10^{-7}$; Supporting Information Fig. S10).

In Hispanics/Latinas, we did not find any genome-wide significant association signals for either GWEIS (Table 5). The top two loci in the GWEIS of stressful life events were rs58707171 ($P = 3.02 \times 10^{-7}$) and rs6579218 ($P = 4.94 \times 10^{-7}$) (Supporting Information Fig. S11). The top two loci in the GWEIS of social support were rs35612712 ($P = 3.42 \times 10^{-7}$) and rs61973969 ($P = 9.41 \times 10^{-7}$) (Supporting Information Fig. S12).

REPLICATION SAMPLES: GWEIS

No top variants were significant in any replication sample (Table 6).

SECONDARY ANALYSES

The top loci in African Americans did not have similarly low *P*-values in Hispanics/Latinas and vice versa (see Supporting Information). Rerunning the GWAS after including the environmental exposures did not systematically change the results (see Supporting Information). SNP heritability estimates for depressive symptoms and the environmental exposures were low (less than 10%) when each was examined on its own and only significant for stressful life events, after adjusting for covariates (Table 7). The numerically largest and statistically significant estimate was found for stressful life events (8%). Interestingly, a very large genetic correlation was detected in the bivariate REML for depressive symptoms and stressful life events (rG = 0.95; $P = 0.04$) after adjusting for covariates, suggesting that the genetic influences on depressive symptoms and stressful life events are largely shared. Indeed, after adjusting for each environmental measure in the REML analysis, no significant heritable signal for depressive symptoms remained. The GWAS and GWEIS results using a nonparametric bootstrap were similar to our original findings (see Supporting Information), suggesting our results were not sensitive to distributional assumptions.

DISCUSSION

This study involved two major innovations in efforts to identify the genetic basis of depression. First, to our knowledge, this was the first genome-wide GxE analysis of depression. Prior GxE studies have focused on a relatively limited set of candidate gene polymorphisms, many of which have showed mixed results.[10,68] Second, our study was also the largest GWAS of depressive symptoms conducted specifically in African Americans and Hispanics/Latinas. To our knowledge, only one prior GWAS was conducted among these groups; this study had a much smaller sample (African Americans $n = 1{,}603$; Hispanics $n = 1{,}443$) and did not examine GxE.[69]

We highlight three findings. First, although no genome-wide significant loci were detected in our

TABLE 2. Replication of genome-wide association study (GWAS) results for the top loci ($P < 1 \times 10^{-5}$) in African Americans

			WHI		HRS					GTP					Discovery: WHI ($n = 7{,}179$)			Replication: HRS ($n = 1{,}231$)			Replication: GTP ($n = 2{,}010$)		
SNP	Chr	Position	A1	A2	G/I	Info	MAF	A1	A2	G/I	Info	MAF	A1	A2	β	SE	P-value	β	SE	P-value	β	SE	P-value
rs73531535	16	20105038	C	T	I	0.995	0.245	C	T	I	0.973	0.246	T	C	−0.297	0.055	5.75×10^{-8}	0.060	0.106	0.573	−0.325	0.452	0.472
rs75407252	3	54241886	C	T	I	0.922	0.051	C	T	I	0.868	0.048	T	C	−0.548	0.110	6.99×10^{-7}	0.285	0.208	0.171	0.241	0.969	0.804
rs11233283	11	82415904	A	G	I	0.999	0.192	A	G	I	0.968	0.185	A	G	−0.298	0.062	1.41×10^{-6}	0.194	0.117	0.098	−0.015	0.504	0.976
rs34257140	17	42675053	G	T	G	1	0.102	G	T	I	0.971	0.106	T	G	−0.313	0.065	1.59×10^{-6}	0.112	0.152	0.461	−0.131	0.639	0.838
rs580112	3	177289895	A	G	I	0.999	0.158	A	G	I	0.985	0.152	A	G	0.279	0.060	2.84×10^{-6}	−0.130	0.123	0.290	0.120	0.539	0.824
rs1413154	13	83240729	G	T	G	1	0.219	G	T	G	0.987	0.223	T	G	−0.283	0.061	3.54×10^{-6}	0.141	0.105	0.181	−0.024	0.465	0.959
rs1893586	21	43286918	A	G	I	0.999	0.462	A	G	I	0.993	0.478	A	G	0.211	0.046	4.19×10^{-6}	−0.046	0.094	0.626	−0.281	0.385	0.465
rs10777901	12	98492992	A	C	G	1	0.498	A	C	G	1.018	0.476	A	C	0.206	0.045	4.27×10^{-6}	0.155	0.090	0.085	0.220	0.381	0.563
rs10125319	9	133426729	C	T	I	0.996	0.495	C	T	I	1.008	0.487	T	C	−0.214	0.047	4.27×10^{-6}	−0.039	0.089	0.664	−0.408	0.382	0.286
rs10221121	16	56840328	A	G	G	1	0.230	A	G	G	1.001	0.210	A	G	−0.241	0.053	5.98×10^{-6}	−0.020	0.109	0.857	−0.448	0.472	0.343
rs210329	14	54059800	G	T	I	0.996	0.303	G	T	I	0.970	0.283	T	G	0.217	0.048	6.35×10^{-6}	−0.018	0.101	0.856	0.346	0.436	0.427
rs28493952	3	95747804	C	T	I	0.979	0.291	C	T	I	0.936	0.295	T	C	0.234	0.052	6.41×10^{-6}	0.065	0.104	0.530	0.736	0.435	0.091
rs7312307	12	106441333	C	G	I	0.982	0.090	C	G	I	0.927	0.091	C	G	0.376	0.084	6.92×10^{-6}	0.124	0.162	0.447	−0.674	0.694	0.331
rs17030391	2	43353504	A	G	I	0.998	0.122	A	G	I	0.961	0.132	A	G	0.316	0.071	7.84×10^{-6}	−0.009	0.143	0.947	−0.142	0.579	0.806
rs4866976	5	45579793	A	G	I	0.989	0.076	A	G	I	0.943	0.082	A	G	−0.361	0.081	8.04×10^{-6}	0.205	0.171	0.230	−1.304	0.719	0.070
rs418207	3	9225376	A	G	G	1	0.486	A	G	G	1.029	0.494	A	G	−0.219	0.050	9.59×10^{-6}	−0.228	0.093	0.015	0.030	0.378	0.938

HRS, Health and Retirement Study. These models were estimated using R 3.0.1. Covariates in HRS were age, income, education, marital status and the top 10 principal components. Imputation was conducted using IMPUTE2.

GTP, Grady Trauma Project. In these analyses with dosage data, PLINK models A1 as the tested allele. SNPs were analyzed using additive coding, where allele dosages were analyzed. Covariates in the GTP were age, income per month, education, marital status, and five principal components. In the GTP, quality control and imputation were performed by the PGC Statistical Analysis Group. Methods for imputation are described in the Supporting Information.

The Bonferroni adjusted α level in these analyses was $0.05/16 = 0.003$.

TABLE 3. Replication of genome-wide association study (GWAS) results for the top loci ($P < 1 \times 10^{-5}$) in Hispanics

			WHI		HCHS/SOL					Discovery: WHI ($n = 3{,}138$)			Replication: HCHS/SOL ($n = 3{,}371$)		
SNP	Chr	Position	A1	A2	G/I	Info	MAF	A1	A2	β	SE	*P*-value	β	SE	*P*-value
rs2532087	4	15878327	C	G	I	0.926	0.210	C	G	0.538	0.104	2.44×10^{-7}	0.556	0.215	0.00964
rs4542757	18	50198724	C	T	G	1.000	0.415	C	T	−0.413	0.083	7.31×10^{-7}	−0.072	0.174	0.68
rs10249677	7	50650831	G	T	I	0.979	0.065	T	G	1.050	0.216	1.20×10^{-6}	−0.582	0.354	0.1
rs1129411	2	231077725	A	G	G	1.000	0.084	A	G	0.664	0.142	2.94×10^{-6}	0.262	0.305	0.39
rs11738766	5	8214282	A	G	G	1.000	0.286	A	G	−0.413	0.089	3.11×10^{-6}	−0.277	0.191	0.147
rs34359572	1	194036781	A	G	I	0.999	0.083	A	G	−0.747	0.162	4.10×10^{-6}	−0.019	0.311	0.951
rs609508	20	54167720	C	G	I	0.998	0.215	C	G	0.443	0.097	5.21×10^{-6}	0.069	0.208	0.738
rs16823787	2	183692791	A	G	I	0.987	0.091	A	G	0.659	0.144	5.21×10^{-6}	−0.099	0.297	0.739
rs17345417	4	95948486	A	G	I	0.996	0.102	A	G	−0.574	0.126	5.30×10^{-6}	0.194	0.284	0.495
rs2822657	21	15774729	C	T	G	1.000	0.436	T	C	−0.366	0.080	5.35×10^{-6}	−0.098	0.171	0.569
rs13033587	2	52857818	C	T	I	0.997	0.489	T	C	0.376	0.083	5.85×10^{-6}	0.298	0.174	0.0869
rs9601962	13	83312889	G	T	I	0.973	0.210	T	G	0.494	0.110	6.91×10^{-6}	0.098	0.211	0.644
rs2282123	6	89907561	C	G	I	0.995	0.238	C	G	0.411	0.092	7.19×10^{-6}	0.049	0.202	0.808
rs10886733	10	122402887	C	T	I	0.989	0.106	T	C	0.556	0.124	7.23×10^{-6}	0.054	0.272	0.843
rs61848143	10	24746704	C	G	I	0.985	0.175	G	C	−0.502	0.112	7.85×10^{-6}	0.410	0.223	0.0662
rs10166852	2	183450923	C	G	I	0.989	0.471	C	G	−0.375	0.084	7.85×10^{-6}	0.141	0.176	0.423
rs6736484	2	45146524	G	T	I	0.948	0.068	G	T	−0.721	0.162	9.05×10^{-6}	−0.285	0.338	0.399
rs2912513	8	69968166	A	T	I	0.999	0.035	A	T	−0.996	0.224	9.33×10^{-6}	−0.119	0.472	0.8

HCHS/SOL, Hispanic Community Health Study/Study of Latinos. These models were estimated using a linear mixed model fit by maximum likelihood with age, education, study center, five principal components, and covariates adjusting for the sampling design. Imputation was conducted using IMPUTE2. In HCHS/SOL, A1 was the tested allele. The Bonferroni adjusted α level in these analyses was $0.05/18 = 0.003$.

TABLE 4. Genome-wide by environment interaction study (GWEIS) results for the top loci ($P < 1 \times 10^{-6}$) in African Americans

									SNP main effect			SNP × environment interaction term				
SNP	Chr	Position	G/I	Info	MAF	A1	A2	Freq1	β	SE	*P*-value	β	SE	*P*-value	Location	Closest gene (<20 kb)
Stressful Life Event Results ($n = 6{,}982$)																
rs4652467	1	180097705	I	0.945	0.026	A	G	0.026	−0.662	0.167	1	0.691	0.111	4.10×10^{-10}		*CEP350*
rs7275997	21	19663487	G	0.993	0.180	A	G	0.820	0.264	0.069	1	−0.278	0.053	1.22×10^{-7}	Intron variant	*TMPRSS15*
rs28377528	7	153884444	I	0.874	0.420	A	G	0.580	−0.212	0.058	1	0.237	0.046	3.23×10^{-7}	Intron variant	*DPP6*
rs2852310	18	43093004	I	0.996	0.027	A	G	0.027	−0.560	0.183	1	0.617	0.123	4.66×10^{-7}	Intron variant	*SLC14A2*
rs12183135	6	151353805	G	0.996	0.024	C	G	0.024	−0.137	0.155	1	0.491	0.100	8.01×10^{-7}		*MTHFD1L*
Social Support Results ($n = 6{,}908$)																
rs77966298	2	10984514	I	0.891	0.034	A	G	0.966	0.796	0.223	1	−0.592	0.115	2.43×10^{-7}		*PDIA6*
rs6419121	4	88490040	I	0.921	0.178	C	G	0.178	−0.375	0.096	1	0.280	0.055	3.98×10^{-7}		
rs10836421	11	35581792	I	0.971	0.315	A	G	0.315	−0.184	0.071	1	0.217	0.043	4.34×10^{-7}		
rs78012311	21	33634345	I	0.981	0.104	C	G	0.104	0.468	0.094	1	−0.321	0.065	8.23×10^{-7}		*MIS18A*

Robust (sandwich) standard errors are presented. In these tests of statistical interaction (on the additive scale and using allele dosages), probABEL uses A2 as the tested (nonreference) allele. The β coefficients in these models can be interpreted as follows. For stressful life events, for example, the SNP main effect β coefficient indicates the average difference in levels of depressive symptoms for women with a zero value on all covariates, who have 1 copy of the tested allele, and who are in the lowest quartile of stressful life events. The GxE interaction term indicates the average estimated difference in the effect of each tested allele on depressive symptoms associated with a one-unit different in stressful life events, adjusting for covariates. The Bonferroni adjusted α level in these analyses was 2.5×10^{-8}.

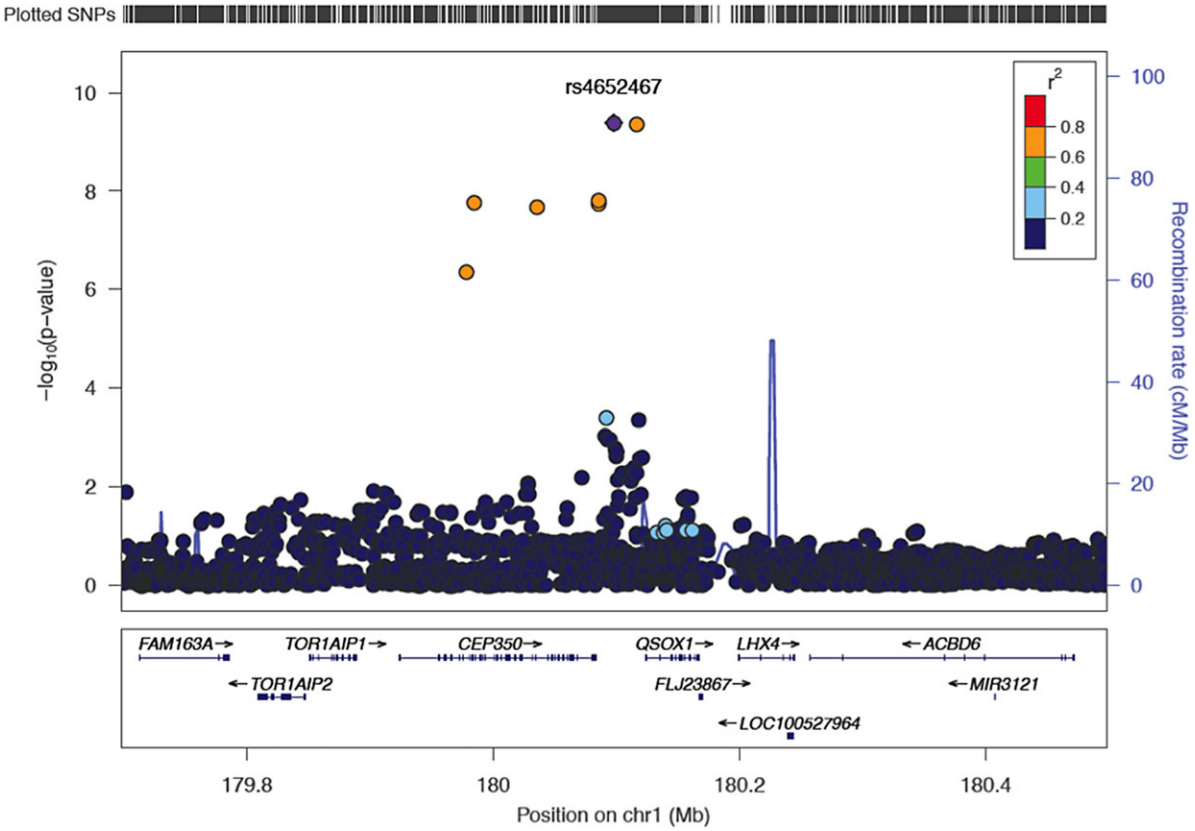

Figure 1. Regional association plot for the top SNP (rs4652467) identified in the African American genome-wide by environment interaction study (GWEIS) of stressful life events. The regional association plot was generated using LocusZoom (http://csg.sph.umich.edu/locuszoom/). We present results for the African American reference panel only as the SNP was monomorphic in Europeans (100% G allele). 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) and stressful life events (in the test of GxE) and levels of depressive symptoms. SNPs are colored based on the level of linkage disequilibrium (LD) between each SNP and the index SNP. r^2 values are determined based on the HG19/1000 Genomes (March 2012 build) data. The index SNP (rs4652467, purple diamond) and its closest neighbors (shown in orange) are imputed.

GWAS, three of the strongest signals were in genes previously implicated in depression-related phenotypes. In African Americans, our top SNP was located 20 kb from *GPR139*. Recent studies show that GPR139 encodes a highly conserved G-protein-coupled receptor whose ligands are tryptophan and phenylalanine.[70] Expression of GPR139 appears to be restricted to the central system and evidence from mouse studies suggests that it is specifically expressed in the lateral habenula and septum, two regions previously implicated in the pathophysiology of depression.[71] Based on these results, Bonaventure and colleagues suggested that GRP139 may mediate the well-established depressogenic effects of tryptophan depletion.[70] Our second best SNP in African Americans was located in a calcium channel gene (*CACNA2D3*). Variants in calcium channel signaling genes have been associated with MDD and other psychiatric disorders in large-scale genome-wide association studies.[72,73] However, the *CACNA2D3* variant did not show evidence of association in either the GTP or HRS replication samples. In the analysis of Hispanics/Latinas, the second strongest signal was located in *DCC* (deleted in colorectal cancer), which encodes the netrin-1 receptor.[74] *DCC* regulates transmembrane signaling receptor activity and is mutated or downregulated in colorectal cancer and esophageal carcinoma. Manitt and colleagues recently found *DCC* signaling aids in establishing medial prefrontal cortex dopamine synaptic connectivity and that higher expression of DCC may be linked to suicide.[75] The *DCC* variant, however, was not associated with depressive symptoms in our replication sample. However, the *DCC* variant (as well as other top loci) showed similar directions of effect across the discovery and replication results, suggesting that our study may have been underpowered. Indeed, a post-hoc power calculation suggested we had poor power among the top results ($P < 1 \times 10^{-5}$) to detect the effect sizes observed given our discovery sample sizes (African Americans = 7,179; Hispanics = 3,138). Specifically, the average power among the top SNPs was 0.26 in the African American GWAS and 0.23 in the Hispanic discovery GWAS. Thus, it appears that even larger samples sizes

TABLE 5. Genome-wide by environment interaction study (GWEIS) results for the top loci ($P < 1 \times 10^{-6}$) in Hispanics

								SNP main effect			SNP × environment interaction term				
SNP	Chr	Position	G/I	Info	MAF	A1	A2	Freq1	β	SE	P-value	β	SE	P-value	Location	Closest gene (<20 kb)
Stressful Life Event Results ($n = 2{,}989$)																
rs58707171	4	36317832	I	0.921	0.037	A	C	0.963	0.649	0.254	1	−0.778	0.152	3.02×10^{-7}	Intron variant	*DTHD1*
rs6579218	20	33709846	I	0.989	0.156	C	G	0.844	0.425	0.142	1	−0.505	0.100	4.94×10^{-7}	Intron variant	*EDEM2*
rs10227305	7	3272267	I	0.849	0.207	A	C	0.793	0.308	0.133	1	−0.454	0.093	9.36×10^{-7}		
Social Support Results ($n = 3{,}012$)																
rs35612712	4	187347203	I	0.941	0.416	C	T	0.416	−0.375	0.119	1	0.376	0.074	3.42×10^{-7}	Intron variant	*F11-AS1*
rs61973969	13	96689182	I	0.985	0.032	C	T	0.032	−0.979	0.317	1	0.839	0.171	9.41×10^{-7}	Intron variant	*UGGT2*

Robust (sandwich) standard errors are presented. In these tests of statistical interaction (on the additive scale and using allele dosages), probABEL uses A2 as the tested (nonreference) allele. The β coefficients in these models can be interpreted as follows. For stressful life events, for example, the SNP main effect β coefficient indicates the average difference in levels of depressive symptoms for women with a zero value on all covariates, who have 1 copy of the tested allele, and who are in the lowest quartile of stressful life events. The GxE interaction term indicates the average estimated difference in the effect of each tested allele on depressive symptoms associated with a one-unit different in stressful life events, adjusting for covariates. The Bonferroni adjusted α level in these analyses was 2.5×10^{-8}.

are needed to detect SNPs associated with depressive symptoms.

Second, in the African American sample, we observed a genome-wide significant interaction between rs4652467, a variant 14 kb away from *CEP350*, and stressful life events. This interaction suggested depressive symptoms were highest among those with more exposure to stressful life events who also had more copies of the major allele. However, this GxE was not observed in the HRS replication. Whether this lack of replication indicates a spurious GxE result or is due to the differences in WHI and HRS phenotype definitions is unclear. Of note, only three of the six depressive symptoms assessed in WHI were also assessed in HRS; the stressful life events measures also had limited overlap (see Supporting Information for comparisons). The failure to identify more genome-wide significant GxE loci or replicate the one genome-wide significant finding may also be due to the small discovery sample size or smaller size of the HRS sample. Our discovery GWEIS analysis could have been underpowered, especially since GxE studies are known to require even larger samples than primary genetic association studies, perhaps as much as four times the size.[76,77] However, a post-hoc power calculation we ran suggested our discovery GWEIS had high power (>90%) to detect the effect estimates we observed. This power estimate is likely inflated due to Winner's Curse (or the phenomena by which detected effects are larger than they really are)[78] and also does not take into account measurement error. Future studies are needed to identify optimal methods to estimate Winner's curse adjusted effect sizes for GxE interaction effects that also address measurement error.

Third, we were able to estimate the SNP heritability of depressive symptoms as well as the two social-environmental exposures in African Americans. SNP heritability estimates were low (less than 10%) for all three phenotypes. The SNP heritability for depressive symptoms (5%) was numerically the lowest and about one-quarter the size of estimates that have been observed in case-control studies of MDD with European-ancestry samples.[60,61] SNP-chip heritability estimates of other psychiatric and behavioral symptoms have also been shown elsewhere[79,80] to produce similarly lower heritability estimates than those obtained from studies examining disorders. Moreover, the largest and only statistically significant estimate observed was for stressful life events (8%), suggesting there may be some degree of gene-environment correlation. Our SNP heritability estimate for stressful life events was lower than a previous study, which found that SNPs explained 29% of the variance in stressful life events.[81] That study, however, was of European ancestry adults and focused on 6-month, rather than past-year stressors and was drawn from a case-control sample of adults with recurrent MDD. Interestingly, we also found a very large genetic correlation for depressive symptoms with stressful life events (rG = 0.95), suggesting that common variation underlying depressive symptoms and stressful life event

TABLE 6. Replication of genome-wide by environment interaction study (GWEIS) results for the top loci ($P < 1 \times 10^{-6}$) in African Americans and Hispanics

									SNP main effect			SNP × environment interaction term		
SNP	Chr	Position	G/I	Info	MAF	A1	A2	Freq1	β	SE	*P*-value	β	SE	*P*-value
African Americans														
Stressful Life Event Results ($n = 952$)														
rs4652467	1	180097705	I	0.919	0.029	A	G	0.971	0.143	0.310	0.645	−1.227	0.765	0.109
rs7275997	21	19663487	I	0.999	0.176	A	G	0.176	−0.242	0.151	0.109	0.124	0.279	0.655
rs28377528	7	153884444	I	0.960	0.439	A	G	0.439	−0.018	0.116	0.878	0.074	0.206	0.718
rs2852310	18	43093004	I	0.961	0.028	A	G	0.972	0.192	0.273	0.483	0.660	0.422	0.118
rs12183135	6	151353805	I	0.953	0.025	C	G	0.975	−0.693	0.374	0.064	−0.035	0.889	0.969
Social Support Results ($n = 952$)														
rs77966298	2	10984514	I	0.995	0.027	A	G	0.027	0.177	0.686	0.796	−0.073	0.319	0.820
rs6419121	4	88490040	I	0.994	0.177	C	G	0.823	−0.136	0.259	0.598	0.105	0.131	0.422
rs10836421	11	35581792	I	0.998	0.284	A	G	0.716	0.325	0.193	0.092	−0.166	0.100	0.098
rs78012311	21	33634345	I	0.995	0.082	C	G	0.918	0.470	0.343	0.171	−0.243	0.176	0.167
Hispanics														
Stressful Life Event Results ($n = 1{,}117$)														
rs58707171	4	36317832	I	0.992	0.040	A	C	0.960	0.374	0.413	0.365	−0.771	0.788	0.328
rs6579218	20	33709846	I	0.997	0.141	G	C	0.141	0.554	0.241	0.022	0.210	0.411	0.609
rs10227305	7	3272267	G	1	0.196	A	C	0.804	0.115	0.211	0.586	0.233	0.362	0.521
Social Support Results ($n = 1{,}117$)														
rs35612712	4	187347203	I	0.999	0.401	T	C	0.401	−0.026	0.174	0.883	−0.170	0.268	0.525
rs61973969	13	96689182	I	0.998	0.035	T	C	0.035	−0.118	0.458	0.797	0.467	0.706	0.509

The African American replication was performed in HRS, Health and Retirement Study. The Hispanic/Latino replication was performed in HCHS/SOL, Hispanic Community Health Study/Study of Latinos. The Bonferroni adjusted α level in these analyses was $0.05/9 = 0.006$. Robust (sandwich) standard errors were used.

exposure, though modest on their own, were highly overlapping in this sample. This finding could be an artifact of the correlated nature of these variables when assessed in cross-sectional studies. Indeed, stressful life events ($r = 0.32$) and social support ($r = 0.30$) were modestly correlated with depressive symptoms, and thus these GCTA results could reflect shared genetic contribution to self-reported measures. Future studies are needed to replicate these findings and determine the impact of this degree of gene-environment correlation (as well as environment-depression correlation) for studying GxE.

Another area for future research relates to whether and how to adjust for use of antidepressant medications in studies of depressive symptoms. In the current study, we followed the precedent set by the CHARGE consortium,[6] which conducted the largest meta-analysis of depressive symptoms to date, and used an algorithm to modify our depressive symptom score

TABLE 7. Results of genome-wide complex trait analysis based on the GREML method

	Model 1			Model 2		
	V(G)/Vp	SE	*P*	V(G)/Vp	SE	*P*
Depressive symptoms	0.05	0.04	0.07	0.04	0.04	0.16
Stressful life events	0.08	0.04	0.02	0.06	0.04	0.06
Social support	0.04	0.04	0.13	0.03	0.04	0.25
Depressive symptoms, controlling for stress	0.03	0.04	0.18	0.02	0.04	0.29
Depressive symptoms, controlling for support	0.04	0.04	0.11	0.03	0.04	0.19
	rG	SE	*P*	rG	SE	*P*
Depressive symptoms and stressful life events	0.95	0.32	0.01	0.97	0.48	0.04
Depressive symptoms and social support	−0.80	0.45	0.08	−0.79	0.76	0.21

V(G)/Vp = SNP heritability estimate.
rG = bivariate REML analysis.
Model 1: Adjusted for age, principal components, and imputation group.
Model 2: Adjusted for Model 1 covariates and income, education, marital status.
All phenotypes were treated as continuous measures.
P-values for the bivariate REML analysis are one-sided and test whether the genetic correlation between depressive symptoms and each of the two environmental exposures is significantly different from zero.

to account for medication use. By harmonizing our depressive symptoms phenotype to theirs, we aimed to facilitate future replication efforts and increase interpretation of results across individual studies. However, there are certainly many alternative approaches, such as conducting the GWAS and GWEIS analyses after excluding medication users, or accounting for medication use using alternative adjustment algorithms (of note, including antidepressant medication use would not have been appropriate, for reasons outlined in the Supporting Information). Simulation studies are needed to fully evaluate the strengths and drawbacks of alternative approaches. Such studies could evaluate the extent to which different conditions (e.g., the percentage of the sample taking medications, the shape of the distribution of the outcome, the average effect sizes for the efficacy of medications, and differences in the distribution of outcome by medication use) produce different GWAS and GWEIS effect estimates.

As noted, future studies pursuing genome-wide environment interaction will require large samples. In the absence of a large sample, researchers can use several alternative approaches to GWEIS including: (1) testing for GxE with replicable variants identified from GWAS; (2) pursuing two-stage genome-wide GxE[82]; and (3) conducting gene pathway-by-environment interaction analyses [83] or polygenic risk score-by-environment interaction analyses.[84–86]

Several limitations should be noted. First, the outcome was based on a brief inventory of depressive symptoms during the past week, rather than levels of depressive symptoms captured over a longer period of time. Thus, it is unclear how long these symptoms lasted. However, the CES-D has demonstrated excellent psychometric properties, including in predicting DSM-IV diagnoses,[33,34] and its widespread use in epidemiological studies enabled us to conduct discovery and replication analyses. Future studies of trait or diagnostic measures of depressive symptoms in minority populations are needed. Second, the social-environmental exposures included in our GxE analyses were based on retrospective reporting and in the case of stressful life events, only captured the prior year. Thus, our study was not designed to capture whether genetic variation interacted with stressors experienced earlier in the lifespan. Prospective studies examining GxE at different stages of the lifespan are needed. Moreover, stressful life events and social support were assessed concurrently with depressive symptoms in the discovery sample as well as both replications. This may not be ideal, especially when studying the effects of stress, as prior work suggests the odds of depression is greatest in the same month of the stressor.[87] Longitudinal, prospective studies measuring social-environmental exposures antecedent to and close in time to depressive symptoms are necessary. These study designs are particularly important, as prior work suggests support for the 5-HTTLPR G×E, for example, is more consistent when structured interviews of stressful life events are used instead of self-report questionnaires.[88,89] Finally, our replication samples were smaller and more phenotypically heterogeneous than the discovery sample. For example, the WHI and HRS samples were of older adults, GTP comprised mostly middle-aged adults, and HCHS/SOL comprised a broader age range. The phenotypic measures also varied across these samples. Unfortunately, these limitations reflect the state of the field. Harmonizing data for GWAS and GxE analyses on a large scale in racial/ethnic minority populations is challenging. Whether our failure to replicate reflects Type I error in the discovery sample or Type II error in the replication is unknown. By undertaking these analyses, we hope to spark more large-scale epidemiological studies to incorporate such measures and to study the genetic determinants of depression in women, who are more burdened by the disorder than men.

Acknowledgments. The authors thank Stephan Ripke and Laramie Duncan for their assistance in conducting imputation for the Grady Trauma Project replication dataset. The authors also thank the developers of the probABEL software, especially Yurii Aulchenko and Maksim Struchalin, for their guidance in conducting the GxE analyses (http://www.genabel.org).

Research reported in this publication was supported by the National Institute of Mental Health of the National Institutes of Health under Award Number K01MH102403 (E.C.D.) and K24MH094614 (Dr. S.W.-S.) and by a NARSAD Young Investigator Grant from the Brain & Behavior Research Foundation (E.C.D.). 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, HHSN 268201100001C, HHSN268201100002C, HHSN 268201100003C, HHSN268201100004C, and HHSN 271201100004C. HRS is supported by the National Institute on Aging (NIA U01AG009740). The genotyping was funded separately by the National Institute on Aging (RC2 AG036495, RC4 AG039029). Genotyping was conducted by the NIH Center for Inherited Disease Research (CIDR) at Johns Hopkins University. Genotyping quality control and final preparation of the data were performed by the Genetics Coordinating Center at the University of Washington.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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