

Genomewide association studies of suicide attempts in US soldiers

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Suicide is a global public health problem with particular resonance for the US military. Genetic risk factors for suicidality are of interest as indicators of susceptibility and potential targets for intervention. We utilized population-based nonclinical cohorts of US military personnel (discovery: $N = 473$ cases and $N = 9778$ control subjects; replication: $N = 135$ cases and $N = 6879$ control subjects) and a clinical case-control sample of recent suicide attempters ($N = 51$ cases and $N = 112$ control subjects) to conduct GWAS of suicide attempts (SA). Genomewide association was evaluated within each ancestral group (European-, African-, Latino-American) and study using logistic regression models. Meta-analysis of the European ancestry discovery samples revealed a genomewide significant locus in association with SA near *MRAP2* (melanocortin 2 receptor accessory protein 2) and *CEP162* (centrosomal protein 162); 12 genomewide significant SNPs in the region; peak SNP rs12524136-T,

OR = 2.88, $p = 5.24E-10$. These findings were not replicated in the European ancestry subsamples of the replication or suicide attempters samples. However, the association of the peak SNP remained significant in a meta-analysis of all studies and ancestral subgroups (OR = 2.18, 95%CI 1.70, 2.80). Polygenic risk score (PRS) analyses showed some association of SA with bipolar disorder. The association with SNPs encompassing *MRAP2*, a gene expressed in brain and adrenal cortex and involved in neural control of energy homeostasis, points to this locus as a plausible susceptibility gene for suicidality that should be further studied. Larger sample sizes will be needed to confirm and extend these findings.

KEYWORDS

genetics, genomewide association, military, risk, suicide, suicide attempt

1 | INTRODUCTION

Suicide morbidity and mortality constitute a major global public health problem (Whiteford et al., 2013). The age-adjusted death rate from suicide in the United States has climbed steadily for the past 15 years (through 2014, the most recent year for which data are publicly available) and suicide now ranks as the third leading cause of death among older adolescents and young adults ages 15–24 (www.cdc.gov/nchs/faststas/death.htm). Suicide is of particular concern to the US military, where suicide attempts are among the leading causes of injury. Moreover, death by suicide recently surpassed combat casualty as the most frequent cause of death among active-duty Servicemembers (Armed Forces Health Surveillance Center, 2014). Though suicide rates in the US Army have historically been lower than in the general population, this trend has changed in recent years (Anglemyer, Miller, Buttrey, & Whitaker, 2016) leading to intensive suicide prevention efforts (Engel, 2013; Ursano, 2013).

Numerous recent studies have focused on predictors of suicidality in the US military. These studies have tended to converge upon several risk factors shared with the civilian sector (e.g., demographics of young adults, particularly males; depression and other mental disorders, and history of childhood maltreatment; Afifi et al., 2016) and others unique to the military (e.g., deployment experiences) (LeardMann et al., 2013; Nock et al., 2014; Ramsawh et al., 2014; Ursano et al., 2015). This attention to risk factors has extended to genetic and other biological factors (Oquendo et al., 2016; Sudol & Mann, 2017; Turecki, 2014), with the goal of developing a bio-signature for suicide (Oquendo et al., 2014). Recent reports of a combined genetic–epigenetic risk marker for suicidality in *SKA2* (Guintivano et al., 2014; Kaminsky et al., 2015) are of considerable interest, and await further replication in population-based samples, as do other multivariate approaches that incorporate genomic and clinical risk factors (Niculescu, Levey, Phalen, et al., 2015). Although twin studies have documented genetic influences on suicide-related phenotypes (heritability ~30–55%) (Tidemalm et al., 2011), it is clear that suicidality is a multi-determined, genetically complex trait, as is the case for virtually all mental and behavioral disorders (Gelernter, 2015). Thus, a great many genes and genomic processes (e.g., epistasis and

epigenetic variation) are likely to contribute to risk for suicidality, but none have been firmly established (Niculescu, Levey, Le-Niculescu, et al., 2015; Oquendo et al., 2014; Sokolowski, Wasserman, & Wasserman, 2014; Turecki, 2014; Yin et al., 2016).

Several genomewide association studies (GWAS) of suicidality have been reported (Mirkovic et al., 2016), mostly limited to analyses of suicide attempts among patients with mood disorders. In four large GWAS comparing mood disorder patients (bipolar and/or major depressive disorder) with and without a history of suicide attempts, no genomewide significant (GWS) loci were detected (Galfalvy et al., 2015; Perlis et al., 2010; Schosser et al., 2011; Willour et al., 2012). A recent report applying polygenic risk score (PRS) analysis to depressed patients in the RADIANT study across suicidal ideation and suicide attempts found no genetic overlap between those two phenotypes, leading the authors to conclude that the tendency to think about suicide and the tendency to act on suicidal thoughts may be influenced by substantially non-overlapping genetic factors (Mullins et al., 2014). There is only partial overlap in epidemiological risk factors for suicidal ideation and attempts (Nock et al., 2013). Thus, genetic factors influencing these various facets of suicidality may also be different and should be examined separately.

In the present study, we utilized population-based nonclinical cohorts of US military personnel and one clinical sample from the same US military population to conduct GWAS of suicide attempts (SA). We also used genomewide genotype data to examine polygenic risk for SA in relation to Psychiatric Genomics Consortium (PGC) PRS for major depressive disorder (Ripke et al., 2013), bipolar disorder (Psychiatric, 2011), and cross-disorder diagnoses (Cross-Disorder Group of the Psychiatric Genomics et al., 2013).

2 | METHODS

2.1 | Subjects

Data come from several components of the Army Study To Assess Risk and Resilience in Servicemembers (STARRS): *New Soldier Study* (NSS),

Pre-/Post-Deployment Study (PPDS), and *Soldier Health Outcomes Study A* (SHOS-A). Detailed information about the design and conduct of STARRS is available in a separate report (Ursano et al., 2014) and in the Supplemental Materials. Soldiers from the respective studies described below are unique and independent as confirmed by analysis of genetic relatedness.

2.1.1 | New soldier study (NSS)

The NSS was carried out among new soldiers at the start of their basic training at three Army Installations between April 2011 and November 2012. In the NSS, reports of lifetime SA refer to their pre-military experiences. Of 39,784 NSS respondents who completed the Self Administered Questionnaire (SAQ), 33,088 (83.2%) provided blood samples. All cases of reported lifetime suicide attempt (SA) were genotyped. The first 17,868 eligible respondents were 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 [SA], 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 NSS1 respondents with eligible SAQ responses whose blood-extracted DNA was genotyped for GWAS. When the remaining half ($N = 15,220$) of the cohort collection was completed, all cases of PTSD and suicide attempt (SA) were selected for genotyping along with 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 genotyped respondents; we refer to this component of the study as NSS2.

2.1.2 | Pre-/post-deployment survey (PPDS)

The PPDS collected baseline data from US Army soldiers in three Brigade Combat Teams (BCTs) during the first quarter of 2012, within approximately 6 weeks of their upcoming deployment to Afghanistan. A total of 9,949 Soldiers were present for duty in the 3 BCTs; 9,488 (95.3%) consented to participate in the survey with 8,558 (86.0%) providing complete baseline survey responses and consent to link their survey responses to their administrative records. Of these, 7,927 PPDS soldiers with eligible baseline SAQ responses and genomewide data are included here.

2.1.3 | Soldier health outcomes study A (SHOS-A)

The SHOS-A is a clinical case-control study of soldiers hospitalized following an acute suicide attempt. This study compared soldiers who attempted suicide (cases) with non-hospitalized Army controls without lifetime suicide attempts matched on a variety of measures including demographics, general psychiatric distress, and psychiatric disorder. The 95 cases and 168 controls for which DNA samples were available are included.

2.2 | Measures

The SAQ surveyed socio-demographic characteristics including lifetime and past-30-day mental disorders, and an array of potential risk and resilience factors. SHOS-A included additional information about the circumstances of the index suicide attempt.

2.2.1 | Suicidality assessment

Suicidal behaviors were assessed using a version of the Columbia Suicidal Severity Rating Scale (C-SSRS) (Posner et al., 2011) assessing lifetime occurrence of suicide ideation ("Did you ever in your life have thoughts of killing yourself" or "Did you ever wish you were dead or would go to sleep and never wake up?") and, among respondents who reported lifetime suicide ideation, suicide plans ("Did you ever have any intention to act [on these thoughts/on that wish]?") and, if so, "Did you ever think about how you might kill yourself [e.g., taking pills, shooting yourself] or work out a plan of how to kill yourself?") and suicide attempts ("Did you ever make a suicide attempt [i.e., purposefully hurt yourself with at least some intention to die]?"). For the primary analysis, controls are those individuals with no lifetime history of SA (who may or may not have a lifetime history of suicidal ideation).

2.3 | Genetic data collection and procedures

NSS1 and PPDS samples were genotyped using the Illumina OmniExpress+Exome array with additional custom content. NSS2 and SHOS-A samples were genotyped on the Illumina PsychChip. Quality control (QC) of genotype data used standard protocols as described elsewhere (Stein et al., 2016). Relatedness testing was carried out with PLINK v1.90 (Chang et al., 2015) and, for pairs of subjects with $\pi > 0.2$, one member of each relative pair was removed at random.

Genotype imputation was performed with a 2-step pre-phasing/imputation approach with a reference multi-ethnic panel from 1000 Genomes Project (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 performed the following quality control procedure to obtain the genotype data for population assignment (see Supplemental Materials) and principal components analysis (PCA). We retained autosomal SNPs with missing rate < 0.05 ; samples with individual-wise missing rate < 0.02 ; SNPs with missing rate < 0.02 ; and SNPs with missing rate difference between cases and controls < 0.02 . After QC, we merged our study samples with HapMap3 samples. We retained SNPs with MAF ≥ 0.01 and performed LD pruning at $R^2 > 0.02$. Finally, we excluded SNPs in MHC region (Chr 6:25–35 Mb) and Chr 8 inversion (Chr 8:7–13 Mb).

TABLE 1 Sample characteristics for NSSI, NSS2, PPDS, and SHOS-A, by ancestry and lifetime history of suicide attempt

	African ancestry			European ancestry			Latino ancestry		
	Lifetime history of suicide attempt			Lifetime history of suicide attempt			Lifetime history of suicide attempt		
	Overall	Yes	No	Overall	Yes	No	Overall	Yes	No
NSSI	n = 1366	n = 52 (3.8%)	n = 1314 (96.2%)	n = 4722	n = 181 (3.8%)	n = 4541 (96.2%)	n = 1442	n = 47 (3.3%)	n = 1395 (96.7%)
Major depressive episode (n, % yes)	122 (8.9)	15 (28.8)	107 (8.1)	740 (15.7)	91 (50.3)	649 (14.3)	184 (12.8)	19 (40.4)	165 (11.8)
Age (mean [sd])	21 (3.1)	21 (3.9)	21 (3.0)	21 (3.3)	20.1 (2.1)	21 (3.3)	20.9 (3.2)	21.3 (3.5)	20.9 (3.2)
Sex (n, % female)	50 (3.7)	20 (40.0)	30 (2.3)	179 (3.8)	32 (17.9)	147 (3.3)	46 (3.2)	12 (26.1)	34 (2.5)
NSS2	n = 406	n = 31 (7.6%)	n = 375 (92.4%)	n = 1817	n = 130 (7.2%)	n = 1687 (92.8%)	n = 498	n = 32 (6.4%)	n = 466 (93.6%)
Major depressive episode (n, % yes)	68 (16.8)	8 (25.8)	60 (16.0)	384 (21.1)	71 (54.6)	313 (18.6)	75 (15.1)	11 (34.4)	11 (34.4)
Age (mean [sd])	20.4 (3.1)	19.5 (2.0)	20.2 (3.1)	20.2 (3.0)	19.8 (2.7)	20.5 (3.1)	20 (3.0)	19.5 (1.7)	20 (3.0)
Sex (n, % female)	30 (7.4)	10 (33.3)	20 (5.4)	130 (7.2)	25 (19.2)	105 (6.3)	31 (6.2)	8 (25.8)	23 (5.0)
PPDS	n = 840	n = 17 (2.0%)	n = 823 (98%)	n = 4683	n = 89 (1.9%)	n = 4594 (98.1%)	n = 1491	n = 29 (1.9%)	n = 1462 (98.1%)
Major depressive episode (n, % yes)	66 (7.9)	8 (47.1)	58 (7.05)	527 (11.3)	39 (43.8)	488 (10.6)	148 (9.9)	16 (55.2)	132 (9.0)
Age (mean [sd])	27.3 (6.7)	25.6 (5.1)	27.3 (6.7)	25.9 (5.9)	25.9 (5.6)	25.9 (5.9)	25.3 (5.6)	26.1 (5.9)	25.2 (5.6)
Sex (n, % female)	17 (2.0)	5 (29.4)	12 (1.5)	89 (1.9)	12 (13.8)	77 (1.7)	29 (1.9)	3 (10.3)	26 (1.8)
SHOS-A	-	-	-	n = 163	n = 51 (31.3%)	n = 112 (68.7%)	-	-	-
Major depressive episode (n, % yes)	-	-	-	NA	NA	NA	-	-	-
Age (mean [sd])	-	-	-	29.7 (7.0)	27.6 (6.1)	30.6 (7.1)	-	-	-
Sex (n, % female)	-	-	-	50 (30.7)	6 (12.0)	44 (39.3)	-	-	-

NSS, new soldier study; PPDS, pre-/post-deployment study; SHOS-A, soldier health outcomes study-A; sd, standard deviation; NA, not available.

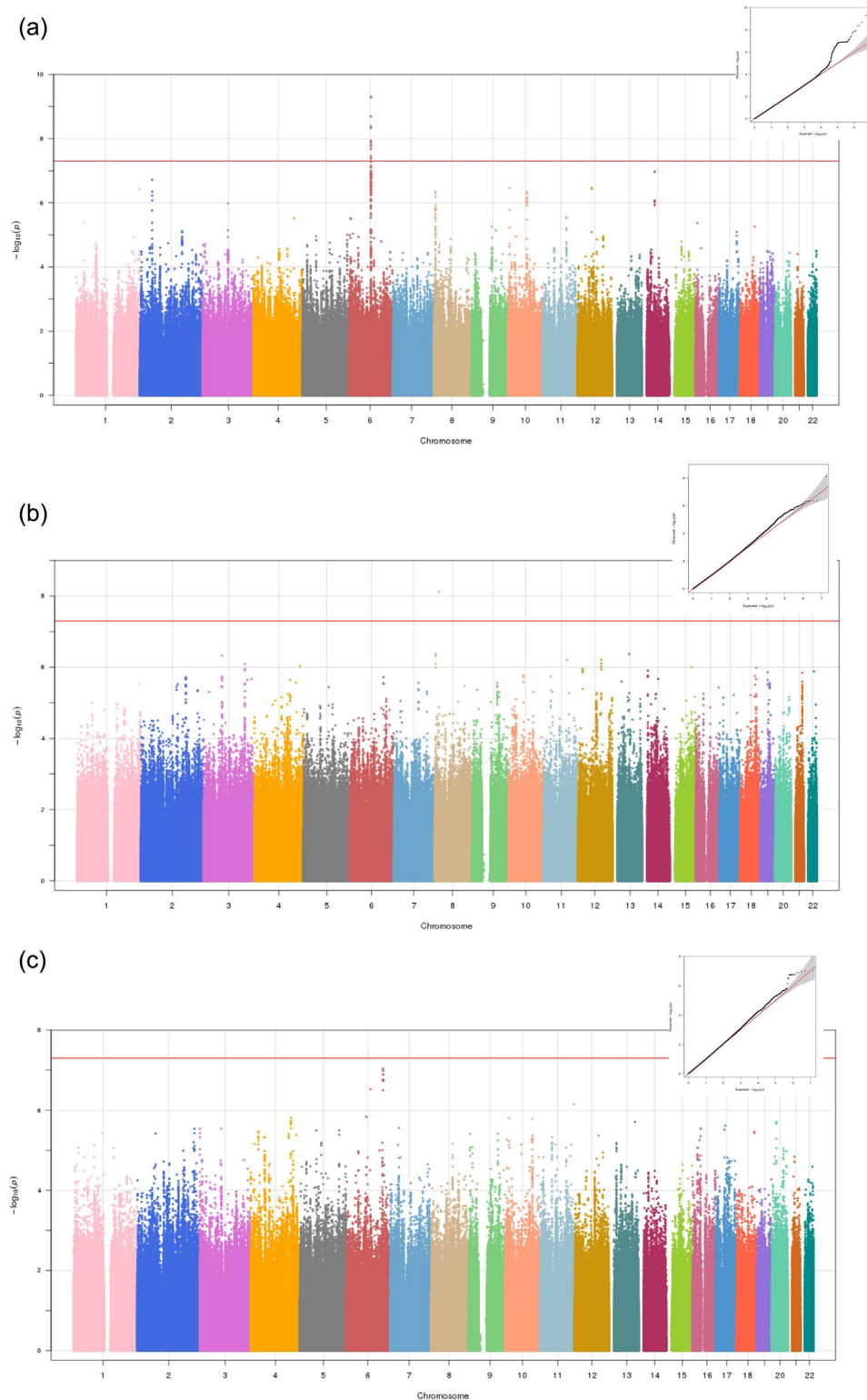


FIGURE 1 Lifetime suicide attempt cases versus non-suicide attempt controls, NSS(1,2). (a) Manhattan plot (left side) and quantile–quantile plot (right side) for genome-wide association study of lifetime suicide attempt, controlling for 10 ethnicity-specific principal components in European (EUR) sample. (b) Manhattan plot (left side) and quantile–quantile plot (right side) for genome-wide association study of lifetime suicide attempt, controlling for ten ethnicity-specific principal components in African (AFR) sample. (c) Manhattan plot (left side) and quantile–quantile plot (right side) for genome-wide association study of lifetime suicide attempt, controlling for ten ethnicity-specific principal components in Latino (LAT) sample [Color figure can be viewed at wileyonlinelibrary.com]

2.4 | Statistical analysis

2.4.1 | Genomewide association study (GWAS)

GWAS were conducted in PLINK v1.90 (Chang et al., 2015) using the logistic regression model, the allelic dosage files generated from imputation, and controlling for PCs 1–10 within ancestry. Since STARRS subjects are from diverse ancestral backgrounds, GWAS were conducted in NSS1 and NSS2 separately within the three ancestral groups (European [EUR], African [AFR], or Latino [LAT]); excluded was an Asian [ASI] group that was too small for separate analysis based on PCs) and then meta-analyzed within ancestry group across both studies. Meta-analysis was conducted using an inverse-weight fixed effects model in PLINK. We filtered out SNPs with MAF < 0.01, imputation quality score (INFO) < 0.8. In order to investigate whether there were multiple independent signals within any meta-analytic regions with several genome-wide significant results, we tested for association between each SNP in the region and the outcome, conditioned on the SNP most significantly associated with the outcome. We used the NSS(1,2) meta-analysis results as our discovery dataset, and tested for consistency of results within PPDS and SHOS-A.

2.4.2 | Polygenic risk scores (PRS)

PRS analyses for the SA phenotype were computed using PLINK in the EUR subsamples only because of the unavailability of reference GWAS data for the other populations with no LD trimming (Chang et al., 2015). *p*-Value thresholds of 0.001, 0.01, 0.05, and 0.3 and 1 were chosen as cutoffs for SNP inclusion in the training samples. The PGC Major Depression, Bipolar Disorder, Schizophrenia, Attention-Deficit/Hyperactivity Disorder, and Cross Disorder analyses were used as the training sample and the PRS was evaluated in NSS(1,2), PPDS, and SHOS-A, combined. Logistic models, controlling for cohort and

within-ethnicity PCs 1–10 were run at each of the five thresholds, for each training/target sample combination. Best call genotypes were created from the 1000G imputation probabilities with imputation quality >0.9 and all available overlapping SNPs between the cohorts and the training samples were used. While we have included PRSs at five different *p*-value thresholds, these scores are highly correlated and straight Bonferroni correction would result in a significance level that is too conservative, we have chosen to use 0.031 as our significance level (assuming the five scores are correlated at $r=0.7$ across the five thresholds). We also conducted a Fisher's test of combined probability across cohorts: $\chi^2_{2k} \sim -2\sum_{i=1}^k \ln(p_i)$.

3 | RESULTS

3.1 | Sociodemographic characteristics and lifetime suicide attempt prevalence

Table 1 shows the case and control counts and their ratio for each study by ancestry. Also included in the table is the proportion of subjects in each group with a lifetime history of major depressive episode(s). Prevalence of lifetime SA in PPDS corresponded to US Army population estimates with approximately 2% lifetime SA. The other samples, which have higher proportions of soldiers with lifetime history of SA, had been purposefully enriched for SA cases, with NSS cases being selected from a larger population and SHOS-A being a clinical study of soldiers with SA.

3.2 | Suicide attempts (SA)

Figure 1a–c shows the results of the SA GWAS meta-analyses of NSS(1,2) in the three ancestral groups; no inflation of test statistics was observed in the GWAS NSS meta-analytic results ($\lambda = 0.98$ –1.00). There was one genome-wide significant (GWS) SNP in the AFR group, rs144662392, $p = 7.65 \times 10^{-9}$, but it was a lone SNP and considered

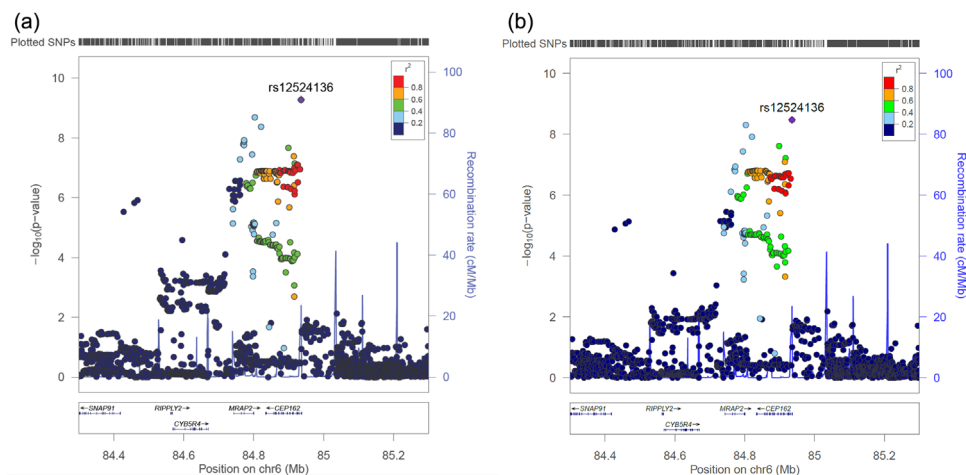


FIGURE 2 Region around genome-wide significant SNPs from the European ancestry NSS(1,2) discovery meta-analysis, chr6:[84303043–85303043], hg19, (a) before adjustment for history of major depressive episode and (b) after adjustment for lifetime history of major depressive episode [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Genome-wide significant SNPs (p -value $< 5 \times 10^{-8}$) from the combined NSS1 and NSS2 European meta-analysis with look-ups in PPDS and SHOS-A soldiers of European ancestry

CHR	BP	SNP	Meta (NSS1 and NSS2)						NSS1			NSS2			PPDS			SHOSA			
			A1	A2	OR	p	FRQ (A1)	OR	p	FRQ (A1)	OR	p	FRQ (A1)	OR	p	FRQ (A1)	OR	p	FRQ (A1)	OR	p
6	84770179	rs2497117	A	G	0.44	1.58E-08	0.95	0.49	9.78E-05	0.39	3.15E-05	0.94	0.39	3.15E-05	0.95	0.85	0.62	0.94	0.85	0.62	0.15
6	84771964	rs2497118	A	G	0.44	1.70E-08	0.95	0.48	8.31E-05	0.38	4.02E-05	0.95	0.38	4.02E-05	0.95	0.80	0.50	0.95	0.80	0.50	0.23
6	84772469	rs2480192	T	C	0.44	1.32E-08	0.95	0.49	1.35E-04	0.37	1.63E-05	0.95	0.37	1.63E-05	0.95	0.79	0.49	0.94	0.79	0.49	0.24
6	84772961	rs2497119	A	C	0.43	1.18E-08	0.95	0.48	9.92E-05	0.37	2.14E-05	0.95	0.37	2.14E-05	0.95	0.78	0.47	0.95	0.78	0.47	0.24
6	84794805	rs142060512 ^a	T	C	2.84	3.55E-08	0.02	2.99	7.43E-06	2.63	1.25E-03	0.02	2.63	1.25E-03	0.02	1.17	0.75	0.03	1.17	0.75	0.22
6	84803043	rs116923768 ^a	A	T	0.30	2.02E-09	0.98	0.26	1.92E-07	0.37	2.01E-03	0.98	0.37	2.01E-03	0.98	0.68	0.44	0.97	0.68	0.44	0.07
6	84809043	chr6_84809043_D ^a	I2	D	0.32	4.68E-09	0.98	0.29	5.44E-07	0.38	1.88E-03	0.97	0.38	1.88E-03	0.97	0.88	0.79	0.97	0.88	0.79	0.09
6	84820786	rs116878613 ^a	T	C	0.30	4.12E-09	0.98	0.27	3.61E-07	0.37	2.24E-03	0.98	0.37	2.24E-03	0.98	0.70	0.47	0.97	0.70	0.47	0.06
6	84898516	rs117975834 ^a	C	G	2.88	2.12E-08	0.02	3.03	6.05E-06	2.68	9.06E-04	0.02	2.68	9.06E-04	0.02	0.93	0.88	0.03	0.93	0.88	0.14
6	84914920	rs78022606	A	G	2.41	4.14E-08	0.04	2.33	5.28E-05	2.54	2.02E-04	0.04	2.54	2.02E-04	0.04	0.75	0.51	0.05	0.75	0.51	0.12
6	84935294	chr6_84935294_D ^a	I5	D	0.35	4.96E-10	0.97	0.37	6.62E-06	0.32	1.69E-05	0.96	0.32	1.69E-05	0.96	1.22	0.67	0.95	1.22	0.67	0.23
6	84935441	rs12524136 ^a	T	C	2.88	5.24E-10	0.03	2.73	6.98E-06	3.10	1.71E-05	0.04	3.10	1.71E-05	0.04	0.82	0.67	0.05	0.82	0.67	0.23

NSS, new soldier study; PPDS, pre- and post-deployment study; SHOS-A, soldier health outcomes study; CHR, chromosome; BP, genomic location in kilobases; SNP, single-nucleotide polymorphism; A1, effect allele; A2, non-effect allele; OR, odds ratio; FRQ, frequency of effect allele in the sample.

We used a threshold of 0.8 for INFO score to filter out any poorly imputed SNPs. All SNPs in this table are imputed. The p -value for the smallest genotyped SNP in that region for the EUR NSS1/2 meta-analysis (rs7741955 A, 84829622) was 2.278e-07 OR = 2.1187. Logistic models adjusted for 10 ancestrally specific principal components.

^aRemained genome-wide significant after controlling for lifetime history of major depressive episode(s).

likely to be a spurious finding. One gene region, all within a span of ~200 K bp located on Chr 6, had several loci with meta-analytic GWS results for SA in the EUR group. Many of the SNPs are in high LD ($r^2 \geq 0.8$). The regional plot in Figure 2a shows that the signal is near the *MRAP2* and *CEP162* (also known as *KIAA1009* or *QN1*) genes on Chr 6. Figure 2b shows that the signal remains with multiple genomewide significant results even when adjusted for lifetime major depression.

Table 2 provides the NSS meta-analyzed GWS results in the NSS(1,2) meta-analysis for the EUR group and their corresponding results in the PPDS and SHOS-A EUR analyses. (Results for these same SNPs in the AFR and LAT samples, none of which are statistically significant, are shown in Supplementary Table S1.) Adjusting for history of lifetime major depressive episode, the NSS(1,2) effects are in the same direction and of similar magnitude, and most remain genomewide significant (Table 2). This suggests that the region is not just operating through major depression to influence SA.

SNP lookups of top results from previous GWAS suicidality studies (Galfalvy et al., 2015; Perlis et al., 2010; Schosser et al., 2011; Willour et al., 2012) showed no statistically significant replication in any of our studies (Supplementary Table S2). We collaborated with the VA Mid-Atlantic MIRECC Workgroup to evaluate our top result in the European ancestry sample of their Iraq-Afghanistan era veteran cohort. (Ashley-Koch et al., 2015) Although our top SNP was not assayed, there is a proxy SNP (rs17187076) in complete LD with our top SNP (rs12524136) in their dataset that was nominally significant ($p = 0.025$; $p = 0.008$ adjusted for lifetime major depressive episode) for lifetime SA. The results for the top EUR GWS SNP (rs12524136) in all studies and ancestral groups is shown as a Forest Plot in Figure 3. The fixed-effects meta-analysis shows an overall statistically significant effect, which appears to be driven by effects in the European subjects.

3.3 | Polygenic risk scores (PRS)

Table 3 presents our analysis of PRS of SA. We used GWAS analyses of MDD (Ripke et al., 2013), bipolar disorder (Psychiatric, 2011), schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics, 2014), attention-deficit/hyperactivity disorder (Neale et al., 2010), and a cross disorder analysis (Cross-Disorder Group of the Psychiatric Genomics et al., 2013) conducted by the international PGC to construct PRS which were then used to predict SA in NSS(1,2), PPDS, and SHOS-A. The PGC-Bipolar disorder PRS showed a relationship with SA in the PPDS and SHOS-A samples (and in a combined cohort analysis [Supplementary Table S3]) at multiple p -value cutoff thresholds (Table 3).

3.4 | Gene-based and pathway analyses

We performed gene and pathway enrichment analyses on the NSS1, NSS2 and PPDS results meta-analyzed for European, African and Latino American samples, without adjustment for MDE. There was no gene showing significant results after Bonferroni correction for the

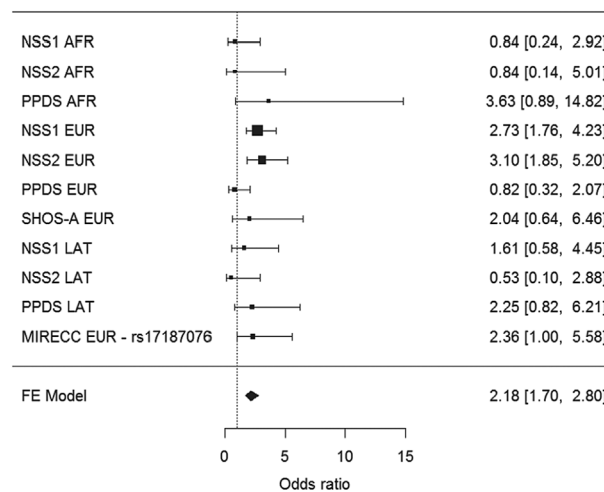


FIGURE 3 Forest plot and fixed effects meta-analysis for lifetime suicide attempt for top SNP in *MRAP2*

number of genes tested ($N = 18,191$) using MAGMA (de Leeuw et al., 2015) (See also Supplemental Materials for pathway analyses).

4 | DISCUSSION

This is, to our knowledge, the first population-based genome-wide association examination of suicide attempts (SA), in the military or otherwise. Whereas a variety of biological risk factors are relatively well established for suicide attempt behavior (Sudol & Mann, 2017), genome-wide association studies provide the opportunity to discover biological systems that had not previously been implicated. Prior genetic association studies of suicidality have relied on clinical or other targeted samples, primarily patients with mood disorders (Galfalvy et al., 2015; Perlis et al., 2010; Schosser et al., 2011; Willour et al., 2012), or patients taking antidepressant medication (Menke et al., 2012; Perroud et al., 2012). Since suicide attempts occur at substantial rates outside of clinically identified samples, examining non-clinical, population-based samples is important to fully understand genetic and other risk factors for SA, which may differ depending on sample characteristics (Mirkovic et al., 2016). We focused on soldiers in the US Army, where better understanding and prevention of suicidality has been a major concern (Engel, 2013; LeardMann et al., 2013; Nock et al., 2014; Ursano et al., 2015).

We identified one GWS region in the EUR NSS(1,2) meta-analysis that includes the genes *CEP162* (involved in ciliary function and mitotic spindle assembly (Leon, Omri, Gely, Klein, & Crisanti, 2006; Wang et al., 2013) and *MRAP2* (melanocortin 2 receptor accessory protein 2), a paralogue of *MRAP*. A role for *CEP162*, involved in required to promote assembly of the transition zone in primary cilia (Wang et al., 2013), cannot be discounted, though it is not an obvious candidate. The product of *MRAP2*, M2CR accessory protein, supports M2CR cell surface expression necessary for the production of a functional ACTH-responsive melanocortin receptor (Chan et al., 2009; Novoselova, Jackson, Campbell, Clark, & Chan, 2013). *MRAP2* is expressed in brain

and adrenal tissue, where it is involved with neural control of energy homeostasis, possibly through *Mrap2* interaction with the melanocortin-4-receptor (*Mc4r*) affecting receptor signaling (Dores, Liang, Davis, Thomas, & Petko, 2016; Jackson, Ramachandrapa, Clark, & Chan, 2015). Loss of *MRAP2* function has been linked to obesity (Asai et al., 2013) but, to the best of our knowledge, has not been previously linked to suicidality or depressive illness. Given the presumed importance of HPA-axis function and glucocorticoid regulation in depressive illness and suicidality, these observations in concert with the findings that rare *MRAP* mutations may cause primary adrenal insufficiency (Guran et al., 2016) suggest that sequencing of this region may yield new insights into the genetic bases for suicidality.

Recent work with polygenic risk scores (PRSs) for suicide attempts in other cohorts has pointed to a role for neurodevelopmental genes (Sokolowski, Wasserman, & Wasserman, 2016), though *MRAP2* or *CEP162*, per se, were not specifically mentioned in that report. We observed an association between a PRS derived from the PGC-bipolar disorder analysis and SA in PPDS and SHOS-A. Although these associations were quite modest and require replication, they are consistent with the hypothesis of shared genetic risk between SA and bipolar disorder. A further caveat in interpreting these PRS associations is that we did not consider bipolar disorder in our case-control definitions. It is therefore conceivable that the PRS associations seen with bipolar disorder and SA may reflect an excess of bipolar disorder in cases. Similarly, although we did adjust for major depressive episode in sensitivity analyses of the EUR sample and found no appreciable decrement in the strength of association with *MRAP2/CEP162*, it is conceivable that other disorders (e.g., PTSD) associated with SA might be confounders of this association. Additional research with larger samples will be needed to exclude this possibility.

Our results should also be interpreted in light of several other limitations. The small sample size and likely heterogeneity may explain the failure to see the GWS results for *MRAP2/CEP162* extend into the PPDS or SHOS-A samples, both of which contained far fewer numbers of SA cases than the NSS discovery sample. The NSS sample, it should be remembered, was based on reporting of SA prior to entering the military. Future studies will need to address this heterogeneity either by stratifying phenotypes differently (e.g., early-onset SA), incorporating informative covariates that may improve power (e.g., childhood maltreatment history or other psychosocial risk factors for SA) (Kaminsky et al., 2015), or attaining much larger sample sizes. Lastly, we recognize that the findings from this study may not generalize beyond military personnel who have self-selected for service and may also have unique experiences as part of military service. Additionally, our sample is mostly male. It may be that the genetic factors influencing suicidality vary by sex, but we lacked the power to test this hypothesis.

In summary, despite this being the largest population-based GWAS study of SA to date, and the first in military population-based cohorts, the number of cases was small. The meta-analytic association of SNPs encompassing *MRAP2*, a gene expressed in brain and adrenal cortex and involved in neural control of energy homeostasis, points to this locus as a credible susceptibility gene for suicidality whose

function should be further studied in larger human subject samples and in animal models of suicidal behaviors (Gould et al., 2017).

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CONFLICTS OF INTEREST

Dr. Stein has in the past 3 years been a consultant for Actelion, Dart Neuroscience, Healthcare Management Technologies, Janssen, Neurocrine Biosciences, Oxeia Biopharmaceuticals, Pfizer, Resilience Therapeutics, and Tonix Pharmaceuticals. Dr. Smoller is an unpaid member of the Scientific Advisory Board of PsyBrain, Inc. In the past three years, Dr. Kessler has been a consultant for Hoffman-La Roche, Inc., Johnson & Johnson Wellness and Prevention, and Sonofi-Aventis Groupe. Dr. Kessler has served on advisory boards for Mensante Corporation, Plus One Health Management, Lake Nona Institute, and U.S. Preventive Medicine. Dr. Kessler owns 25% share in DataStat, Inc. The remaining authors report nothing to disclose.

REFERENCES

- Afifi, T. O., Taillieu, T., Zamorski, M. A., Turner, S., Cheung, K., & Sareen, J. (2016). Association of child abuse exposure with suicidal ideation, suicide plans, and suicide attempts in military personnel and the general population in Canada. *JAMA Psychiatry*, *73*(3), 229–238.
- Anglemyer, A., Miller, M. L., Buttrey, S., & Whitaker, L. (2016). Suicide rates and methods in active duty military personnel, 2005 to 2011: A cohort study. *Annals of Internal Medicine*, *165*(3), 167–174.
- Armed Forces Health Surveillance Center. (2014). Surveillance snapshot: Manner and cause of death, active component, U.S. Armed Forces, 1998–2013. p 21.
- Asai, M., Ramachandrapa, S., Joachim, M., Shen, Y., Zhang, R., Nuthalapati, N., ... Majzoub, J. A. (2013). Loss of function of the melanocortin 2 receptor accessory protein 2 is associated with mammalian obesity. *Science*, *341*(6143), 275–278.
- Ashley-Koch, A. E., Garrett, M. E., Gibson, J., Liu, Y., Dennis, M. F., Kimbrel, N. A., ... Hauser, M. A. (2015). Genome-wide association study of posttraumatic stress disorder in a cohort of Iraq-Afghanistan era veterans. *Journal of Affective Disorders*, *184*, 225–234.
- Chan, L. F., Webb, T. R., Chung, T. T., Meimaridou, E., Cooray, S. N., Guasti, L., ... Clark, A. J. (2009). MRAP and MRAP2 are bidirectional regulators of the melanocortin receptor family. *Proceedings of the National Academy of Sciences of the United States of America* *106*(15), 6146–6151.
- Chang, C. C., Chow, C. C., Tellier, L. C., Vattikuti, S., Purcell, S. M., & Lee, J. J. (2015). Second-generation PLINK: Rising to the challenge of larger and richer datasets. *Gigascience*, *4*, 7.
- Cross-Disorder Group of the Psychiatric Genomics Consortium, Lee, S. H., Ripke, S., Neale, B. M., Faraone, S. V., ... International Inflammatory Bowel Disease Genetics C. (2013). Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nature Genetics*, *45*(9), 984–994.
- de Leeuw, C. A., Mooij, J. M., Heskes, T., & Posthuma, D. (2015). MAGMA: Generalized gene-set analysis of GWAS data. *PLOS Computational Biology*, *11*(4), e1004219.
- Dores, R. M., Liang, L., Davis, P., Thomas, A. L., & Petko, B. (2016). 60 YEARS OF POMC: Melanocortin receptors: Evolution of ligand selectivity for melanocortin peptides. *Journal of Molecular Endocrinology*, *56*(4), T119–T133.
- Engel, C. C. (2013). Suicide, mental disorders, and the US military: Time to focus on mental health service delivery. *JAMA*, *310*(5), 484–485.
- Galfalvy, H., Haghghi, F., Hodgkinson, C., Goldman, D., Oquendo, M. A., Burke, A., ... Mann, J. J. (2015). A genome-wide association study of suicidal behavior. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *168*(7), 557–563.
- Gelernter, J. (2015). Genetics of complex traits in psychiatry. *Biological Psychiatry*, *77*(1), 36–42.
- Gould, T. D., Georgiou, P., Brenner, L. A., Brundin, L., Can, A., Courtet, P., ... Postolache, T. T. (2017). Animal models to improve our understanding and treatment of suicidal behavior. *Translational Psychiatry*, *7*(4), e1092.
- Guintivano, J., Brown, T., Newcomer, A., Jones, M., Cox, O., Maher, B. S., ... Kaminsky, Z. A. (2014). Identification and replication of a combined epigenetic and genetic biomarker predicting suicide and suicidal behaviors. *American Journal of Psychiatry*, *171*(12), 1287–1296.
- Guran, T., Buonocore, F., Saka, N., Ozbek, M. N., Aycan, Z., Bereket, A., ... Achermann, J. C. (2016). Rare causes of primary adrenal insufficiency: Genetic and clinical characterization of a large nationwide cohort. *Journal of Clinical Endocrinology & Metabolism*, *101*(1), 284–292.
- Jackson, D. S., Ramachandrapa, S., Clark, A. J., & Chan, L. F. (2015). Melanocortin receptor accessory proteins in adrenal disease and obesity. *Frontiers in Neuroscience*, *9*, 213.
- Kaminsky, Z., Wilcox, H. C., Eaton, W. W., Van Eck, K., Kilaru, V., Jovanovic, T., ... Smith, A. K. (2015). Epigenetic and genetic variation at SKA2 predict suicidal behavior and post-traumatic stress disorder. *Translational Psychiatry*, *5*, e627.
- LeardMann, C. A., Powell, T. M., Smith, T. C., Bell, M. R., Smith, B., Boyko, E. J., ... Hoge, C. W. (2013). Risk factors associated with suicide in current and former US military personnel. *JAMA*, *310*(5), 496–506.
- Leon, A., Omri, B., Gely, A., Klein, C., & Crisanti, P. (2006). QN1/KIAA1009: A new essential protein for chromosome segregation and mitotic spindle assembly. *Oncogene*, *25*(13), 1887–1895.
- Menke, A., Domschke, K., Czamara, D., Klengel, T., Hennings, J., Lucae, S., ... Binder, E. B. (2012). Genome-wide association study of antidepressant treatment-emergent suicidal ideation. *Neuropsychopharmacology*, *37*(3), 797–807.
- Mirkovic, B., Laurent, C., Podlipski, M. A., Frebourg, T., Cohen, D., & Gerardin, P. (2016). Genetic association studies of suicidal behavior: A review of the past 10 years, progress, limitations, and future directions. *Frontiers in Psychiatry*, *7*, 158.
- Mullins, N., Perroud, N., Uher, R., Butler, A. W., Cohen-Woods, S., Rivera, M., ... Lewis, C. M. (2014). Genetic relationships between suicide attempts, suicidal ideation and major psychiatric disorders: A genome-wide association and polygenic scoring study. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *165B*(5), 428–437.
- Neale, B. M., Medland, S. E., Ripke, S., Asherson, P., Franke, B., Lesch, K. P., ... Psychiatric GCAS. (2010). Meta-analysis of genome-wide association studies of attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, *49*(9), 884–897.
- Niculescu, A. B., Levey, D., Le-Niculescu, H., Niculescu, E., Kurian, S. M., & Salomon, D. (2015). Psychiatric blood biomarkers: Avoiding jumping to premature negative or positive conclusions. *Molecular Psychiatry*, *20*(3), 286–288.

- Niculescu, A. B., Levey, D. F., Phalen, P. L., Le-Niculescu, H., Dainton, H. D., Jain, N., ... Salomon, D. R. (2015). Understanding and predicting suicidality using a combined genomic and clinical risk assessment approach. *Molecular Psychiatry*, 20(11), 1266–1285.
- Nock, M. K., Deming, C. A., Fullerton, C. S., Gilman, S. E., Goldenberg, M., Kessler, R. C., ... Ursano, R. J. (2013). Suicide among soldiers: A review of psychosocial risk and protective factors. *Psychiatry*, 76(2), 97–125.
- Nock, M. K., Stein, M. B., Heeringa, S. G., Ursano, R. J., Colpe, L. J., Fullerton, C. S., ... Kessler, R. C. (2014). Prevalence and correlates of suicidal behavior among soldiers: Results from the army study to assess risk and resilience in servicemembers (Army STARRS). *JAMA Psychiatry*, 71(5), 514–522.
- Novoselova, T. V., Jackson, D., Campbell, D. C., Clark, A. J., & Chan, L. F. (2013). Melanocortin receptor accessory proteins in adrenal gland physiology and beyond. *Journal of Endocrinology*, 217(1), R1–11.
- Oquendo, M. A., Galfalvy, H., Sullivan, G. M., Miller, J. M., Milak, M. M., Sublette, M. E., ... Mann, J. J. (2016). Positron emission tomographic imaging of the serotonergic system and prediction of risk and lethality of future suicidal behavior. *JAMA Psychiatry*, 73(10), 1048–1055.
- Oquendo, M. A., Sullivan, G. M., Sudol, K., Baca-Garcia, E., Stanley, B. H., Sublette, M. E., & Mann, J. J. (2014). Toward a biosignature for suicide. *American Journal of Psychiatry*, 171(12), 1259–1277.
- Perlis, R. H., Huang, J., Purcell, S., Fava, M., Rush, A. J., Sullivan, P. F., ... Smoller, J. W. (2010). Genome-wide association study of suicide attempts in mood disorder patients. *American Journal of Psychiatry*, 167(12), 1499–1507.
- Perroud, N., Uher, R., Ng, M. Y., Guipponi, M., Hauser, J., Henigsberg, N., ... McGuffin, P. (2012). Genome-wide association study of increasing suicidal ideation during antidepressant treatment in the GENDEP project. *The Pharmacogenomics Journal*, 12(1), 68–77.
- Posner, K., Brown, G. K., Stanley, B., Brent, D. A., Yershova, K. V., Oquendo, M. A., ... Mann, J. J. (2011). The Columbia-Suicide Severity Rating Scale: Initial validity and internal consistency findings from three multisite studies with adolescents and adults. *American Journal of Psychiatry*, 168(12), 1266–1277.
- Psychiatric GWAS Consortium Bipolar Disorder Working Group. (2011). Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4. *Nature Genetics*, 43(10), 977–983.
- Ramsawh, H. J., Fullerton, C. S., Mash, H. B., Ng, T. H., Kessler, R. C., Stein, M. B., & Ursano, R. J. (2014). Risk for suicidal behaviors associated with PTSD, depression, and their comorbidity in the U.S. Army. *Journal of Affective Disorders*, 161, 116–122.
- Ripke, S., Wray, N. R., Lewis, C. M., Hamilton, S. P., Weissman, M. M., Breen, G., ... Sullivan, P. F. (2013). A mega-analysis of genome-wide association studies for major depressive disorder. *Molecular Psychiatry*, 18(4), 497–511.
- Schizophrenia Working Group of the Psychiatric Genomics Consortium. (2014). Biological insights from 108 schizophrenia-associated genetic loci. *Nature*, 511(7510), 421–427.
- Schossner, A., Butler, A. W., Ising, M., Perroud, N., Uher, R., Ng, M. Y., ... Lewis, C. M. (2011). Genomewide association scan of suicidal thoughts and behaviour in major depression. *PLoS ONE*, 6(7), e20690.
- Sokolowski, M., Wasserman, J., & Wasserman, D. (2014). Genome-wide association studies of suicidal behaviors: A review. *European Neuropsychopharmacology*, 24(10), 1567–1577.
- Sokolowski, M., Wasserman, J., & Wasserman, D. (2016). Polygenic associations of neurodevelopmental genes in suicide attempt. *Molecular Psychiatry*, 21(10), 1381–1390.
- Stein, M. B., Chen, C. Y., Ursano, R. J., Cai, T., Gelernter, J., Heeringa, S. G., ... Army Study to Assess Risk and Resilience in Servicemembers Collaborators. (2016). Genome-wide association studies of posttraumatic stress disorder in 2 cohorts of US army soldiers. *JAMA Psychiatry*, 73(7), 695–704.
- Sudol, K., & Mann, J. J. (2017). Biomarkers of suicide attempt behavior: Towards a biological model of risk. *Current Psychiatry Reports*, 19(6), 31.
- Tidemalm, D., Runeson, B., Waern, M., Frisell, T., Carlstrom, E., Lichtenstein, P., & Langstrom, N. (2011). Familial clustering of suicide risk: A total population study of 11.4 million individuals. *Psychological Medicine*, 41(12), 2527–2534.
- Turecki, G. (2014). The molecular bases of the suicidal brain. *Nature Reviews Neuroscience*, 15(12), 802–816.
- Ursano, R. J. (2013). Suicide: A national health challenge, an army health threat. *Psychiatry*, 76(2), 95–96.
- Ursano, R. J., Colpe, L. J., Heeringa, S. G., Kessler, R. C., Schoenbaum, M., Stein, M. B., & Army, S. C. (2014). The Army study to assess risk and resilience in servicemembers (Army STARRS). *Psychiatry*, 77(2), 107–119.
- Ursano, R. J., Kessler, R. C., Stein, M. B., Naifeh, J. A., Aliaga, P. A., Fullerton, C. S., ... Army Study to Assess Risk and Resilience in Servicemembers C. (2015). Suicide attempts in the US army during the wars in Afghanistan and Iraq, 2004 to 2009. *JAMA Psychiatry*, 72(9), 917–926.
- Wang, W. J., Tay, H. G., Soni, R., Perumal, G. S., Goll, M. G., Macaluso, F. P., ... Tsou, M. F. (2013). CEP162 is an axoneme-recognition protein promoting ciliary transition zone assembly at the cilia base. *Nature Cell Biology*, 15(6), 591–601.
- Whiteford, H. A., Degenhardt, L., Rehm, J., Baxter, A. J., Ferrari, A. J., Erskine, H. E., ... Vos, T. (2013). Global burden of disease attributable to mental and substance use disorders: Findings from the Global Burden of Disease Study 2010. *Lancet*, 382(9904), 1575–1586.
- Willour, V. L., Seifuddin, F., Mahon, P. B., Jancic, D., Pirooznia, M., Steele, J., ... Potash, J. B. (2012). A genome-wide association study of attempted suicide. *Molecular Psychiatry*, 17(4), 433–444.
- Yin, H., Pantazatos, S. P., Galfalvy, H., Huang, Y. Y., Rosoklija, G. B., Dwork, A. J., ... Mann, J. J. (2016). A pilot integrative genomics study of GABA and glutamate neurotransmitter systems in suicide, suicidal behavior, and major depressive disorder. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 171B(3), 414–426.

SUPPORTING INFORMATION

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