Research Article

Genomewide Association Studies of Suicide Attempts in US Soldiers

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ABSTRACT

Suicide is a global public health problem with particular resonance for the U.S. 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*

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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 [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 et al. 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 and 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 et al. 2015b]. 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 et al. 2015a; Oquendo et al. 2014; Sokolowski 0000-0003-3931-1810 et al. 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].

METHODS

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.

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.

Pre/Post Deployment Survey (PPDS). The PPDS collected baseline data from U.S. Army soldiers in three Brigade Combat Teams (BCTs) during the first quarter of 2012, within approximately six 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.

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.

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.

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).

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 Ilumina 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 π of >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 6:25-35Mb) and Chr 8 inversion (Chr 8:7-13Mb).

Statistical Analysis

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.

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: $X^2_{2k} \sim -2\sum_{i=1}^{k}\ln(p_i)$.

RESULTS

Table 1 about here

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.

Table 2 and Figures 1-2 about here

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 (λ= 0.98-1.00). There was one genome-wide significant (GWS) SNP in the AFR group, rs144662392, p = 7.65 x 10^{-9}, but it was a lone SNP and considered likely to be a spurious finding. One gene region, all within a span of ~ 200K 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.

Table 3 about here

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**).

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

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 and 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 et al. 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 et al. 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 et al. 2016; Jackson et al. 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 et al. 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].

References

Afifi TO, Taillieu T, Zamorski MA, 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 ML, Buttrey S, Whitaker L. 2016. Suicide Rates and Methods in Active Duty Military Personnel, 2005 to 2011: A Cohort Study. Ann Intern Med 165(3):167-174.

Asai M, Ramachandrappa S, Joachim M, Shen Y, Zhang R, Nuthalapati N, Ramanathan V, Strochlic DE, Ferket P, Linhart K, Ho C, Novoselova TV, Garg S, Ridderstrale M, Marcus C, Hirschhorn JN, Keogh JM, O'Rahilly S, Chan LF, Clark AJ, Farooqi IS, Majzoub JA. 2013. Loss of function of the melanocortin 2 receptor accessory protein 2 is associated with mammalian obesity. Science 341(6143):275-278.

Ashley-Koch AE, Garrett ME, Gibson J, Liu Y, Dennis MF, Kimbrel NA, Veterans Affairs Mid-Atlantic Mental Illness Research E, Clinical Center W, Beckham JC, Hauser MA. 2015. Genome-wide association study of posttraumatic stress disorder in a cohort of Iraq-Afghanistan era veterans. J Affect Disord 184:225-234.

Center AFHS. 2014. Surveillance Snapshot: Manner and cause of death, active component, U.S. Armed Forces, 1998-2013. p 21.

Chan LF, Webb TR, Chung TT, Meimaridou E, Cooray SN, Guasti L, Chapple JP, Egertova M, Elphick MR, Cheetham ME, Metherell LA, Clark AJ. 2009. MRAP and MRAP2 are bidirectional regulators of the melanocortin receptor family. Proc Natl Acad Sci U S A 106(15):6146-6151.

Chang CC, Chow CC, Tellier LC, Vattikuti S, Purcell SM, Lee JJ. 2015. Second-generation PLINK: rising to the challenge of larger and richer datasets. Gigascience 4:7.

Cross-Disorder Group of the Psychiatric Genomics C, Lee SH, Ripke S, Neale BM, Faraone SV, Purcell SM, Perlis RH, Mowry BJ, Thapar A, Goddard ME, Witte JS, Absher D, Agartz I, Akil H, Amin F, Andreassen OA, Anjorin A, Anney R, Anttila V, Arking DE, Asherson P, Azevedo MH, Backlund L, Badner JA, Bailey AJ, Banaschewski T, Barchas JD, Barnes MR, Barrett TB, Bass N, Battaglia A, Bauer M, Bayes M, Bellivier F, Bergen SE, Berrettini W,

Betancur C, Bettecken T, Biederman J, Binder EB, Black DW, Blackwood DH, Bloss CS, Boehnke M, Boomsma DI, Breen G, Breuer R, Bruggeman R, Cormican P, Buccola NG, Buitelaar JK, Bunney WE, Buxbaum JD, Byerley WF, Byrne EM, Caesar S, Cahn W, Cantor RM, Casas M, Chakravarti A, Chambert K, Choudhury K, Cichon S, Cloninger CR, Collier DA, Cook EH, Coon H, Cormand B, Corvin A, Coryell WH, Craig DW, Craig IW, Crosbie J, Cuccaro ML, Curtis D, Czamara D, Datta S, Dawson G, Day R, De Geus EJ, Degenhardt F, Djurovic S, Donohoe GJ, Doyle AE, Duan J, Dudbridge F, Duketis E, Ebstein RP, Edenberg HJ, Elia J, Ennis S, Etain B, Fanous A, Farmer AE, Ferrier IN, Flickinger M, Fombonne E, Foroud T, Frank J, Franke B, Fraser C, Freedman R, Freimer NB, Freitag CM, Friedl M, Frisen L, Gallagher L, Gejman PV, Georgieva L, Gershon ES, Geschwind DH, Giegling I, Gill M, Gordon SD, Gordon-Smith K, Green EK, Greenwood TA, Grice DE, Gross M, Grozeva D, Guan W, Gurling H, De Haan L, Haines JL, Hakonarson H, Hallmayer J, Hamilton SP, Hamshere ML, Hansen TF, Hartmann AM, Hautzinger M, Heath AC, Henders AK, Herms S, Hickie IB, Hipolito M, Hoefels S, Holmans PA, Holsboer F, Hoogendijk WJ, Hottenga JJ, Hultman CM, Hus V, Ingason A, Ising M, Jamain S, Jones EG, Jones I, Jones L, Tzeng JY, Kahler AK, Kahn RS, Kandaswamy R, Keller MC, Kennedy JL, Kenny E, Kent L, Kim Y, Kirov GK, Klauck SM, Klei L, Knowles JA, Kohli MA, Koller DL, Konte B, Korszun A, Krabbendam L, Krasucki R, Kuntsi J, Kwan P, Landen M, Langstrom N, Lathrop M, Lawrence J, Lawson WB, Leboyer M, Ledbetter DH, Lee PH, Lencz T, Lesch KP, Levinson DF, Lewis CM, Li J, Lichtenstein P, Lieberman JA, Lin DY, Linszen DH, Liu C, Lohoff FW, Loo SK, Lord C, Lowe JK, Lucae S, MacIntyre DJ, Madden PA, Maestrini E, Magnusson PK, Mahon PB, Maier W, Malhotra AK, Mane SM, Martin CL, Martin NG, Mattheisen M, Matthews K, Mattingsdal M, McCarroll SA, McGhee KA, McGough JJ, McGrath PJ, McGuffin P, McInnis MG, McIntosh A, McKinney R, McLean AW, McMahon FJ, McMahon WM, McQuillin A, Medeiros H, Medland SE, Meier S, Melle I, Meng F, Meyer J, Middeldorp CM, Middleton L, Milanova V, Miranda A, Monaco AP, Montgomery GW, Moran JL, Moreno-De-Luca D, Morken G, Morris DW, Morrow EM, Moskvina V, Muglia P, Muhleisen TW, Muir WJ, Muller-Myhsok B, Murtha M, Myers RM, Myin-Germeys I, Neale MC, Nelson SF, Nievergelt CM, Nikolov I, Nimgaonkar V, Nolen WA, Nothen MM, Nurnberger JI, Nwulia EA, Nyholt DR, O'Dushlaine C, Oades RD, Olincy A, Oliveira G, Olsen L, Ophoff RA, Osby U, Owen MJ, Palotie A, Parr JR, Paterson AD, Pato CN, Pato MT, Penninx BW, Pergadia

ML, Pericak-Vance MA, Pickard BS, Pimm J, Piven J, Posthuma D, Potash JB, Poustka F, Propping P, Puri V, Quested DJ, Quinn EM, Ramos-Quiroga JA, Rasmussen HB, Raychaudhuri S, Rehnstrom K, Reif A, Ribases M, Rice JP, Rietschel M, Roeder K, Roeyers H, Rossin L, Rothenberger A, Rouleau G, Ruderfer D, Rujescu D, Sanders AR, Sanders SJ, Santangelo SL, Sergeant JA, Schachar R, Schalling M, Schatzberg AF, Scheftner WA, Schellenberg GD, Scherer SW, Schork NJ, Schulze TG, Schumacher J, Schwarz M, Scolnick E, Scott LJ, Shi J, Shilling PD, Shyn SI, Silverman JM, Slager SL, Smalley SL, Smit JH, Smith EN, Sonuga-Barke EJ, St Clair D, State M, Steffens M, Steinhausen HC, Strauss JS, Strohmaier J, Stroup TS, Sutcliffe JS, Szatmari P, Szelinger S, Thirumalai S, Thompson RC, Todorov AA, Tozzi F, Treutlein J, Uhr M, van den Oord EJ, Van Grootheest G, Van Os J, Vicente AM, Vieland VJ, Vincent JB, Visscher PM, Walsh CA, Wassink TH, Watson SJ, Weissman MM, Werge T, Wienker TF, Wijsman EM, Willemsen G, Williams N, Willsey AJ, Witt SH, Xu W, Young AH, Yu TW, Zammit S, Zandi PP, Zhang P, Zitman FG, Zollner S, Devlin B, Kelsoe JR, Sklar P, Daly MJ, O'Donovan MC, Craddock N, Sullivan PF, Smoller JW, Kendler KS, Wray NR, International Inflammatory Bowel Disease Genetics C. 2013. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. Nat Genet 45(9):984-994.

de Leeuw CA, Mooij JM, Heskes T, Posthuma D. 2015. MAGMA: generalized gene-set analysis of GWAS data. PLoS Comput Biol 11(4):e1004219.

Dores RM, Liang L, Davis P, Thomas AL, Petko B. 2016. 60 YEARS OF POMC: Melanocortin receptors: evolution of ligand selectivity for melanocortin peptides. J Mol Endocrinol 56(4):T119-133.

Engel CC. 2013. Suicide, mental disorders, and the US military: time to focus on mental health service delivery. Jama 310(5):484-485.

Galfalvy H, Haghighi F, Hodgkinson C, Goldman D, Oquendo MA, Burke A, Huang YY, Giegling I, Rujescu D, Bureau A, Turecki G, Mann JJ. 2015. A genome-wide association study of suicidal behavior. Am J Med Genet B Neuropsychiatr Genet 168(7):557-563.

Gelernter J. 2015. Genetics of Complex Traits in Psychiatry. Biol Psychiatry 77(1):36-42.

Gould TD, Georgiou P, Brenner LA, Brundin L, Can A, Courtet P, Donaldson ZR, Dwivedi Y, Guillaume S, Gottesman, II, Kanekar S, Lowry CA, Renshaw PF, Rujescu D, Smith EG, Turecki G, Zanos P, Zarate CA, Jr., Zunszain PA, Postolache TT. 2017. Animal models to

improve our understanding and treatment of suicidal behavior. Transl Psychiatry 7(4):e1092.

Guintivano J, Brown T, Newcomer A, Jones M, Cox O, Maher BS, Eaton WW, Payne JL, Wilcox HC, Kaminsky ZA. 2014. Identification and replication of a combined epigenetic and genetic biomarker predicting suicide and suicidal behaviors. Am J Psychiatry 171(12):1287-1296.

Guran T, Buonocore F, Saka N, Ozbek MN, Aycan Z, Bereket A, Bas F, Darcan S, Bideci A, Guven A, Demir K, Akinci A, Buyukinan M, Aydin BK, Turan S, Agladioglu SY, Atay Z, Abali ZY, Tarim O, Catli G, Yuksel B, Akcay T, Yildiz M, Ozen S, Doger E, Demirbilek H, Ucar A, Isik E, Ozhan B, Bolu S, Ozgen IT, Suntharalingham JP, Achermann JC. 2016. Rare Causes of Primary Adrenal Insufficiency: Genetic and Clinical Characterization of a Large Nationwide Cohort. J Clin Endocrinol Metab 101(1):284-292.

Jackson DS, Ramachandrappa S, Clark AJ, Chan LF. 2015. Melanocortin receptor accessory proteins in adrenal disease and obesity. Front Neurosci 9:213.

Kaminsky Z, Wilcox HC, Eaton WW, Van Eck K, Kilaru V, Jovanovic T, Klengel T, Bradley B, Binder EB, Ressler KJ, Smith AK. 2015. Epigenetic and genetic variation at SKA2 predict suicidal behavior and post-traumatic stress disorder. Transl Psychiatry 5:e627.

LeardMann CA, Powell TM, Smith TC, Bell MR, Smith B, Boyko EJ, Hooper TI, Gackstetter GD, Ghamsary M, Hoge CW. 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, Baune BT, Arolt V, Muller-Myhsok B, Holsboer F, Binder EB. 2012. Genome-wide association study of antidepressant treatment-emergent suicidal ideation. Neuropsychopharmacology 37(3):797-807.

Mirkovic B, Laurent C, Podlipski MA, 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. Front Psychiatry 7:158.

Mullins N, Perroud N, Uher R, Butler AW, Cohen-Woods S, Rivera M, Malki K, Euesden J, Power RA, Tansey KE, Jones L, Jones I, Craddock N, Owen MJ, Korszun A, Gill M, Mors O, Preisig M, Maier W, Rietschel M, Rice JP, Muller-Myhsok B, Binder EB, Lucae S, Ising M, Craig

IW, Farmer AE, McGuffin P, Breen G, Lewis CM. 2014. Genetic relationships between suicide attempts, suicidal ideation and major psychiatric disorders: a genome-wide association and polygenic scoring study. Am J Med Genet B Neuropsychiatr Genet 165B(5):428-437.

Neale BM, Medland SE, Ripke S, Asherson P, Franke B, Lesch KP, Faraone SV, Nguyen TT, Schafer H, Holmans P, Daly M, Steinhausen HC, Freitag C, Reif A, Renner TJ, Romanos M, Romanos J, Walitza S, Warnke A, Meyer J, Palmason H, Buitelaar J, Vasquez AA, Lambregts-Rommelse N, Gill M, Anney RJ, Langely K, O'Donovan M, Williams N, Owen M, Thapar A, Kent L, Sergeant J, Roeyers H, Mick E, Biederman J, Doyle A, Smalley S, Loo S, Hakonarson H, Elia J, Todorov A, Miranda A, Mulas F, Ebstein RP, Rothenberger A, Banaschewski T, Oades RD, Sonuga-Barke E, McGough J, Nisenbaum L, Middleton F, Hu X, Nelson S, Psychiatric GCAS. 2010. Meta-analysis of genome-wide association studies of attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 49(9):884-897.

Niculescu AB, Levey D, Le-Niculescu H, Niculescu E, Kurian SM, Salomon D. 2015a. Psychiatric blood biomarkers: avoiding jumping to premature negative or positive conclusions. Mol Psychiatry 20(3):286-288.

Niculescu AB, Levey DF, Phalen PL, Le-Niculescu H, Dainton HD, Jain N, Belanger E, James A, George S, Weber H, Graham DL, Schweitzer R, Ladd TB, Learman R, Niculescu EM, Vanipenta NP, Khan FN, Mullen J, Shankar G, Cook S, Humbert C, Ballew A, Yard M, Gelbart T, Shekhar A, Schork NJ, Kurian SM, Sandusky GE, Salomon DR. 2015b. Understanding and predicting suicidality using a combined genomic and clinical risk assessment approach. Mol Psychiatry.

Nock MK, Deming CA, Fullerton CS, Gilman SE, Goldenberg M, Kessler RC, McCarroll JE, McLaughlin KA, Peterson C, Schoenbaum M, Stanley B, Ursano RJ. 2013. Suicide among soldiers: a review of psychosocial risk and protective factors. Psychiatry 76(2):97-125.

Nock MK, Stein MB, Heeringa SG, Ursano RJ, Colpe LJ, Fullerton CS, Hwang I, Naifeh JA, Sampson NA, Schoenbaum M, Zaslavsky AM, Kessler RC. 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 TV, Jackson D, Campbell DC, Clark AJ, Chan LF. 2013. Melanocortin receptor accessory proteins in adrenal gland physiology and beyond. J Endocrinol 217(1):R1-11.

Oquendo MA, Galfalvy H, Sullivan GM, Miller JM, Milak MM, Sublette ME, Cisneros-Trujillo S, Burke AK, Parsey RV, Mann JJ. 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 MA, Sullivan GM, Sudol K, Baca-Garcia E, Stanley BH, Sublette ME, Mann JJ. 2014. Toward a biosignature for suicide. Am J Psychiatry 171(12):1259-1277.

Perlis RH, Huang J, Purcell S, Fava M, Rush AJ, Sullivan PF, Hamilton SP, McMahon FJ, Schulze TG, Potash JB, Zandi PP, Willour VL, Penninx BW, Boomsma DI, Vogelzangs N, Middeldorp CM, Rietschel M, Nothen M, Cichon S, Gurling H, Bass N, McQuillin A, Hamshere M, Wellcome Trust Case Control Consortium Bipolar Disorder G, Craddock N, Sklar P, Smoller JW. 2010. Genome-wide association study of suicide attempts in mood disorder patients. Am J Psychiatry 167(12):1499-1507.

Perroud N, Uher R, Ng MY, Guipponi M, Hauser J, Henigsberg N, Maier W, Mors O, Gennarelli M, Rietschel M, Souery D, Dernovsek MZ, Stamp AS, Lathrop M, Farmer A, Breen G, Aitchison KJ, Lewis CM, Craig IW, 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 GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, Currier GW, Melvin GA, Greenhill L, Shen S, Mann JJ. 2011. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry 168(12):1266-1277.

Psychiatric GCBDWG. 2011. Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4. Nat Genet 43(10):977-983.

Ramsawh HJ, Fullerton CS, Mash HB, Ng TH, Kessler RC, Stein MB, Ursano RJ. 2014. Risk for suicidal behaviors associated with PTSD, depression, and their comorbidity in the U.S. Army. J Affect Disord 161:116-122.

Ripke S, Wray NR, Lewis CM, Hamilton SP, Weissman MM, Breen G, Byrne EM, Blackwood DH, Boomsma DI, Cichon S, Heath AC, Holsboer F, Lucae S, Madden PA, Martin NG, McGuffin P, Muglia P, Noethen MM, Penninx BP, Pergadia ML, Potash JB, Rietschel M, Lin D,

Muller-Myhsok B, Shi J, Steinberg S, Grabe HJ, Lichtenstein P, Magnusson P, Perlis RH, Preisig M, Smoller JW, Stefansson K, Uher R, Kutalik Z, Tansey KE, Teumer A, Viktorin A, Barnes MR, Bettecken T, Binder EB, Breuer R, Castro VM, Churchill SE, Coryell WH, Craddock N, Craig IW, Czamara D, De Geus EJ, Degenhardt F, Farmer AE, Fava M, Frank J, Gainer VS, Gallagher PJ, Gordon SD, Goryachev S, Gross M, Guipponi M, Henders AK, Herms S, Hickie IB, Hoefels S, Hoogendijk W, Hottenga JJ, Iosifescu DV, Ising M, Jones I, Jones L, Jung-Ying T, Knowles JA, Kohane IS, Kohli MA, Korszun A, Landen M, Lawson WB, Lewis G, Macintyre D, Maier W, Mattheisen M, McGrath PJ, McIntosh A, McLean A, Middeldorp CM, Middleton L, Montgomery GM, Murphy SN, Nauck M, Nolen WA, Nyholt DR, O'Donovan M, Oskarsson H, Pedersen N, Scheftner WA, Schulz A, Schulze TG, Shyn SI, Sigurdsson E, Slager SL, Smit JH, Stefansson H, Steffens M, Thorgeirsson T, Tozzi F, Treutlein J, Uhr M, van den Oord EJ, Van Grootheest G, Volzke H, Weilburg JB, Willemsen G, Zitman FG, Neale B, Daly M, Levinson DF, Sullivan PF. 2013. A mega-analysis of genome-wide association studies for major depressive disorder. Mol Psychiatry 18(4):497-511.

Schizophrenia Working Group of the Psychiatric Genomics C. 2014. Biological insights from 108 schizophrenia-associated genetic loci. Nature 511(7510):421-427.

Schosser A, Butler AW, Ising M, Perroud N, Uher R, Ng MY, Cohen-Woods S, Craddock N, Owen MJ, Korszun A, Jones L, Jones I, Gill M, Rice JP, Maier W, Mors O, Rietschel M, Lucae S, Binder EB, Preisig M, Perry J, Tozzi F, Muglia P, Aitchison KJ, Breen G, Craig IW, Farmer AE, Muller-Myhsok B, McGuffin P, Lewis CM. 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. Eur Neuropsychopharmacol 24(10):1567-1577.

Sokolowski M, Wasserman J, Wasserman D. 2016. Polygenic associations of neurodevelopmental genes in suicide attempt. Mol Psychiatry 21(10):1381-1390.

Stein MB, Chen CY, Ursano RJ, Cai T, Gelernter J, Heeringa SG, Jain S, Jensen KP, Maihofer AX, Mitchell C, Nievergelt CM, Nock MK, Neale BM, Polimanti R, Ripke S, Sun X, Thomas ML, Wang Q, Ware EB, Borja S, Kessler RC, Smoller JW, Army Study to Assess R, Resilience in Servicemembers C. 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 JJ. 2017. Biomarkers of Suicide Attempt Behavior: Towards a Biological Model of Risk. Curr Psychiatry Rep 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. Psychol Med 41(12):2527-2534.

Turecki G. 2014. The molecular bases of the suicidal brain. Nat Rev Neurosci 15(12):802-816.

Ursano RJ. 2013. Suicide: a national health challenge, an army health threat. Psychiatry 76(2):95-96.

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

Ursano RJ, Kessler RC, Stein MB, Naifeh JA, Aliaga PA, Fullerton CS, Sampson NA, Kao TC, Colpe LJ, Schoenbaum M, Cox KL, Heeringa SG, Army Study to Assess R, 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 WJ, Tay HG, Soni R, Perumal GS, Goll MG, Macaluso FP, Asara JM, Amack JD, Tsou MF. 2013. CEP162 is an axoneme-recognition protein promoting ciliary transition zone assembly at the cilia base. Nat Cell Biol 15(6):591-601.

Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE, Charlson FJ, Norman RE, Flaxman AD, Johns N, Burstein R, Murray CJ, 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 VL, Seifuddin F, Mahon PB, Jancic D, Pirooznia M, Steele J, Schweizer B, Goes FS, Mondimore FM, Mackinnon DF, Bipolar Genome Study C, Perlis RH, Lee PH, Huang J, Kelsoe JR, Shilling PD, Rietschel M, Nothen M, Cichon S, Gurling H, Purcell S, Smoller JW, Craddock N, DePaulo JR, Jr., Schulze TG, McMahon FJ, Zandi PP, Potash JB. 2012. A genome-wide association study of attempted suicide. Mol Psychiatry 17(4):433-444.

Yin H, Pantazatos SP, Galfalvy H, Huang YY, Rosoklija GB, Dwork AJ, Burke A, Arango V, Oquendo MA, Mann JJ. 2016. A pilot integrative genomics study of GABA and glutamate neurotransmitter systems in suicide, suicidal behavior, and major depressive disorder. Am J Med Genet B Neuropsychiatr Genet 171B(3):414-426.

Figure Legends

Figure 1: Lifetime suicide attempt cases vs. 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 ten 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

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

Figure 3. Forest Plot and Fixed Effects Meta-Analysis for Lifetime Suicide Attempt for Top SNP in *MRAP2*

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

	African Ancestry			European Ancestry			
		Lifetime history of suicide attempt			Lifetime history of suicide attempt		
	Overall	Yes	No	Overall	Yes	No	Ov
NSS1	**n = 1366**	**n = 52 (3.8%)**	**n = 1314 (96.2%)**	**n = 4722**	**n = 181 (3.8%)**	**n = 4541 (96.2%)**	**n =**
Major depressive episode (n, % yes)	122 (8.9)	15 (28.8)	107 (8.1)	740 (15.7)	91 (50.3)	649 (14.3)	184
Age (mean (sd))	21 (3.1)	21 (3.9)	21 (3.0)	21 (3.3)	20.1 (2.1)	21 (3.3)	20.9
Sex (n, % female)	50 (3.7)	20 (40.0)	30 (2.3)	179 (3.8)	32 (17.9)	147 (3.3)	46
NSS2	**n = 406**	**n = 31 (7.6%)**	**n = 375 (92.4%)**	**n = 1817**	**n = 130 (7.2%)**	**n = 1687 (92.8%)**	**n =**
Major depressive episode (n, % yes)	68 (16.8)	8 (25.8)	60 (16.0)	384 (21.1)	71 (54.6)	313 (18.6)	75 (
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

Sex (n, % female)	30 (7.4)	10 (33.3)	20 (5.4)	130 (7.2)	25 (19.2)	105 (6.3)	31
PPDS	**n = 840**	**n = 17 (2.0%)**	**n = 823 (98%)**	**n = 4683**	**n = 89 (1.9%)**	**n = 4594 (98.1%)**	**n =**
Major depressive episode (n, % yes)	66 (7.9)	8 (47.1)	58 (7.05	527 (11.3)	39 (43.8)	488 (10.6)	148
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
Sex (n, % female)	17 (2.0)	5 (29.4)	12 (1.5)	89 (1.9)	12 (13.8)	77 (1.7)	29
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

Table 2. Genome-wide significant SNPs (p-value < $5x10^{-8}$) from the combined NSS1 and NSS2 European meta-analysis with look-ups in PPDS and SHOS-A soldiers of European ancestry.

					Meta (NSS1 and NSS2)		**NSS1**			**NSS2**			**PPDS**			**SHOSA**		
CHR	**BP**	**SNP**	**A1**	**A2**	**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	0.94	0.39	3.15E-05	0.95	0.85	0.62	0.94	0.46	0.15
6	84771964	rs2497118	A	G	0.44	1.70E-08	0.95	0.48	8.31E-05	0.95	0.38	4.02E-05	0.95	0.80	0.50	0.95	0.52	0.23
6	84772469	rs2480192	T	C	0.44	1.32E-08	0.95	0.49	1.35E-04	0.95	0.37	1.63E-05	0.95	0.79	0.49	0.94	0.53	0.24
6	84772961	rs2497119	A	C	0.43	1.18E-08	0.95	0.48	9.92E-05	0.95	0.37	2.14E-05	0.95	0.78	0.47	0.95	0.52	0.24
6	84794805	rs142060512*	T	C	2.84	3.55E-08	0.02	2.99	7.43E-06	0.03	2.63	1.25E-03	0.02	1.17	0.75	0.03	2.31	0.22
6	84803043	rs116923768*	A	T	0.30	2.02E-09	0.98	0.26	1.92E-07	0.98	0.37	2.01E-03	0.98	0.68	0.44	0.97	0.24	0.07
6	84809043	chr6_84809043_D*	I2	D	0.32	4.68E-09	0.98	0.29	5.44E-07	0.97	0.38	1.88E-03	0.97	0.88	0.79	0.97	0.27	0.09
6	84820786	rs116878613*	T	C	0.30	4.12E-09	0.98	0.27	3.61E-07	0.98	0.37	2.24E-03	0.98	0.70	0.47	0.97	0.23	**0.06**
6	84898516	rs117975834*	C	G	2.88	2.12E-08	0.02	3.03	6.05E-06	0.03	2.68	9.06E-04	0.02	0.93	0.88	0.03	2.72	0.14
6	84914920	rs78022606	A	G	2.41	4.14E-08	0.04	2.33	5.28E-05	0.04	2.54	2.02E-04	0.04	0.75	0.51	0.05	2.38	0.12
6	84935294	chr6_84935294_D*	I5	D	0.35	4.96E-10	0.97	0.37	6.62E-06	0.96	0.32	1.69E-05	0.96	1.22	0.67	0.95	0.49	0.23

6	84935441	rs12524136*	T	C	2.88	5.24E-10	0.03	2.73	6.93E-06	0.04	3.10	1.71E-05	0.04	0.82	0.67	0.05	2.04	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.

*Remained genome-wide significant after controlling for lifetime history of major depressive episode(s)

Table 3. Polygenic Risk Score (PRS) Analysis in Subjects of European Ancestry

PRS cutoff: P-value threshold for GWAS SNPs to enter the PGS. **P-value**: PRS p-value in logistic model adjusted for PC1-PC10. **R^2**: Nagelkerke's R^2 model fit for PRS model with 10 PCs and an indicator for cohort [NSS1,2; PPDS; SHOSA]. **Nsnps**: number of SNPs. PRS were created with no LD trimming from best guess genotypes with imputation quality > 0.9. Association p-values < 0.031 are in red.

NSS: New Soldier Study; PPDS: Pre/Post Deployment Study; SHOS-A: Soldier Health Outcomes Study A; PGC: Psychiatric Genomics Consortium; MDD: Major Depressive Disorder

		Suicide Attempt													
		NSS(1,2)					**PPDS**					**SHOSA**			
	PRS cutoff	**0.001**	**0.01**	**0.05**	**0.3**	**1**	**0.001**	**0.01**	**0.05**	**0.3**	**1**	**0.001**	**0.01**	**0.05**	**0.3**
PGC MDD	P-value	0.3	0.65	0.58	0.64	0.46	0.53	0.37	0.23	0.07	0.09	0.41	0.21	0.08	0.05
	R^2	5.06E-04	9.79E-05	1.50E-04	1.03E-04	2.59E-04	5.09E-04	9.96E-04	1.76E-03	3.82E-03	3.55E-03	5.52E-03	1.28E-02	2.64E-02	3.29E-02
	Nsnps	1561	14070	62852	346855	1105624	1561	14070	62852	346855	1105624	1561	14070	62852	346855
PGC Bipolar Disorder	P-value	0.29	0.36	0.83	0.72	0.67	0.05	0.27	**0.01**	**0.02**	**0.01**	0.69	0.38	0.14	**0.03**
	R^2	5.34E-04	4.08E-04	2.11E-05	6.29E-05	8.50E-05	5.01E-03	1.50E-03	9.29E-03	6.58E-03	7.66E-03	1.33E-03	6.49E-03	1.79E-02	4.02E-02
	Nsnps	5717	36099	139094	667426	1992362	5717	36099	139094	667426	1992362	5717	36099	139094	667426
PGC Cross Disorder	P-value	0.82	0.77	0.8	0.76	0.62	0.74	0.82	0.73	0.72	0.76	0.22	0.17	0.1	0.09
	R^2	2.43E-05	4.26E-05	3.12E-05	4.57E-05	1.16E-04	1.45E-04	7.55E-05	1.55E-04	1.68E-04	1.27E-04	1.28E-02	1.59E-02	2.27E-02	2.45E-02
	Nsnps	4397	22898	82811	379334	1115985	4397	22898	82811	379334	1115985	4397	22898	82811	379334
PGC ADHD	P-value	0.58	0.35	0.55	0.55	0.73	0.10	0.19	0.52	0.35	0.42	0.74	0.31	0.55	0.09
	R^2	1.49E-04	4.13E-04	1.71E-04	1.73E-04	5.89E-05	3.38E-03	2.13E-03	5.21E-04	1.10E-03	8.00E-04	8.73E-04	8.58E-03	2.89E-03	2.35E-02
	Nsnps	1374	12229	57681	332494	1088226	1374	12229	57681	332494	1088226	1374	12229	57681	332494

PGC Schizophrenia	P-value	0.57	0.94	0.45	0.34	0.35	0.46	0.96	0.73	0.29	0.31	0.46	0.43	0.19	0.07
	R^2	1.54E-04	2.50E-06	2.72E-04	4.32E-04	4.28E-04	6.93E-04	1.27E-05	1.56E-04	1.42E-03	1.28E-03	4.59E-03	5.12E-03	1.42E-02	2.82E-02
	Nsnps	5563	26709	91163	393174	1117574	5563	26709	91163	393174	1117574	5563	26709	91163	393174

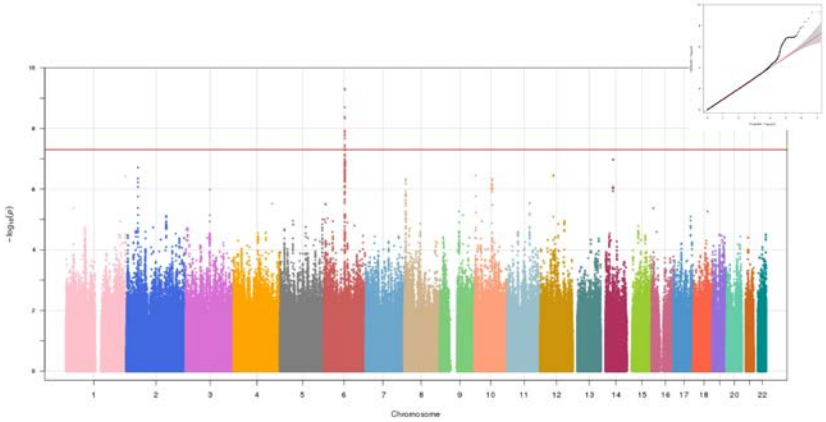


Figure 1a

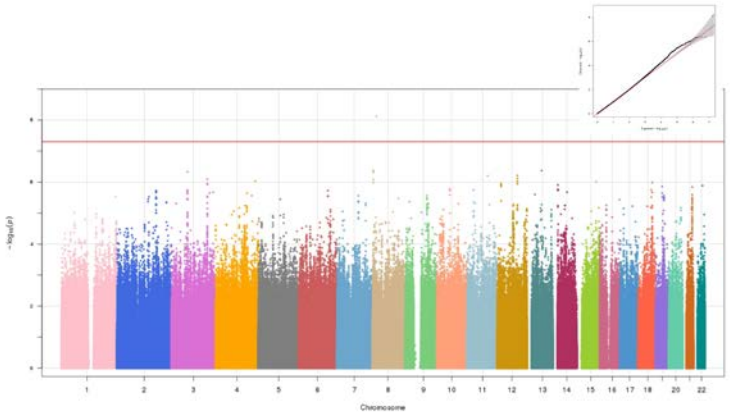


Figure 1b

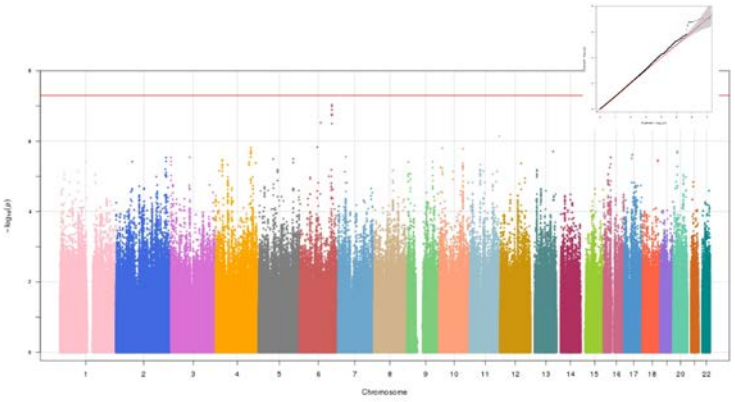
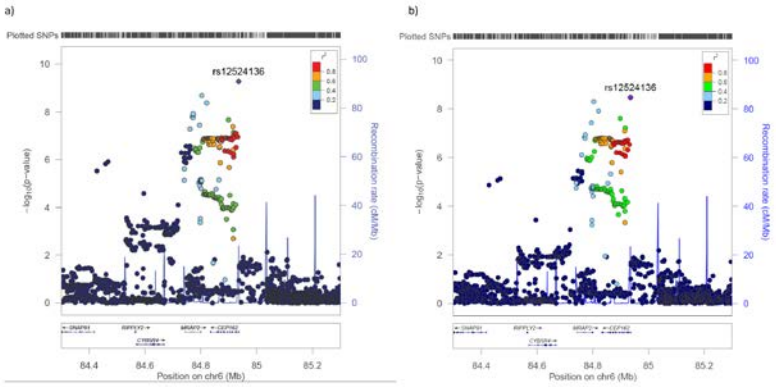
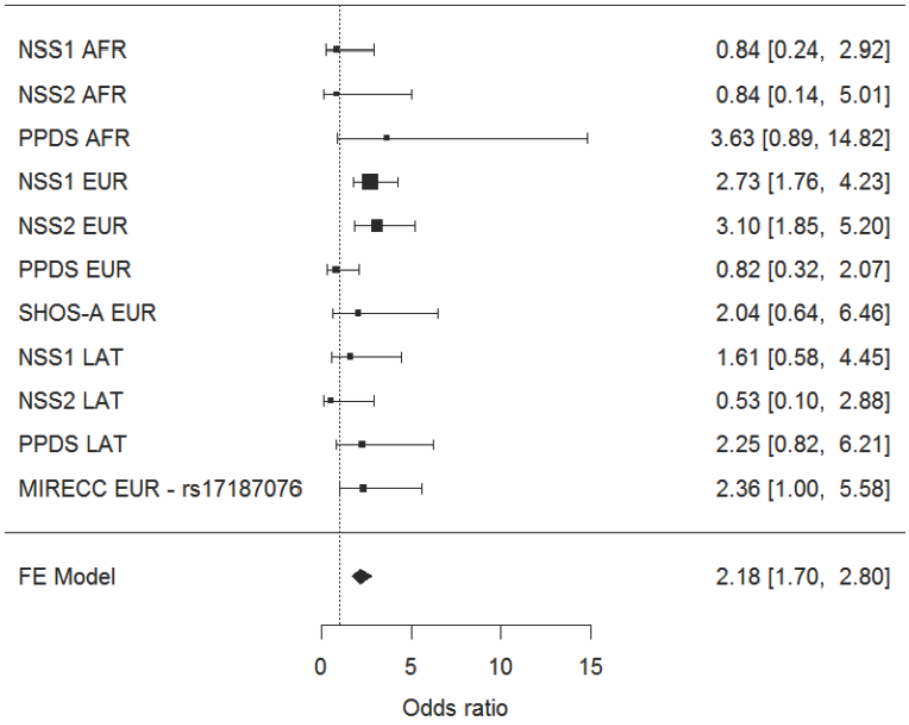


Figure 1c



SNP with lowest p-value is a deletion and therefore the index SNP (purple diamond) is the non-insertion/deletion with the lowest p-value.
chr6:[84303043–85303043], hg19, 1000 Genomes imputation.

Figure 2



*NOTE: In MIRECC EUR sample, rs12524136 was not available so rs17187076 which is in 100% LD with rs12524136 was used as a proxy.

Figure 3