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Authors

Stein, Murray

Jain, Sonia

Campbell-Sills, Laura

et al.

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Polygenic Risk for Major Depression is Associated with Lifetime Suicide Attempt in US Soldiers Independent of Personal and Parental History of Major Depression

Murray B. Stein, MD, MPH[1,3,*], **Sonia Jain, PhD**[3], **Laura Campbell-Sills, PhD**[1], **Erin B. Ware, PhD**[4], **Karmel W. Choi, PhD**[5], **Feng He**[3], **Tian Ge, PhD**[5], **Joel Gelernter, MD**[6], **Jordan W Smoller, MD,ScD**[5], **Ronald C. Kessler, PhD**[7], **Robert J. Ursano, MD**[8]

[1]Department of Psychiatry, University of California, San Diego, La Jolla, CA

[2]VA San Diego Healthcare System, San Diego, CA

[3]Herbert Wertheim School of Public Health and Human Longevity Science, University of California, San Diego, La Jolla, CA

[4]Institute for Social Research, University of Michigan, Ann Arbor, MI, USA

[5]Psychiatric and Neurodevelopmental Genetics Unit, Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA USA

[6]Departments of Psychiatry, Genetics, and Neuroscience, Yale University School of Medicine, New Haven, CT, USA

[7]Department of Health Care Policy, Harvard Medical School, Boston, MA, USA

[8]Center for the Study of Traumatic Stress, Department of Psychiatry, Uniformed Services University of the Health Sciences, Bethesda, MD, USA

Abstract

Background: Suicide is a major public health problem. The contribution of common genetic variants for MDD independent of personal and parental history of MDD has not been established.

[*]Corresponding Author: Murray B. Stein MD, MPH, Department of Psychiatry and School of Public Health, University of California San Diego, 9500 Gilman Drive, La Jolla, CA, 92093-0855 (mstein@health.ucsd.edu).

Author Contributions:

1 Conception or design of the work (Stein, Campbell-Sills, Choi, Ursano)
2 Data collection (Stein, Kessler, Ursano).
3 Data analysis and interpretation (Stein, Jain, Choi, He, Ge)
4 Drafting the article (Stein, Campbell-Sills, Choi, Ware, Ursano).
5 Critical revision of the article (all authors)
6 Final approval of the version to be published (all authors).

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Methods: Polygenic risk score (using PRS-CS) for MDD was calculated for US Army soldiers of European ancestry. Associations between polygenic risk for MDD and lifetime suicide attempt (SA) were tested in models that also included parental or personal history of MDD. Models were adjusted for age, sex, tranche (where applicable) and 10 principal components reflecting ancestry.

Results: In the first cohort, 417 (6.3%) of 6573 soldiers reported a lifetime history of SA. In a multivariable model that included personal [OR=3.83, 95% CI:3.09–4.75] and parental history of MDD [OR=1.43, 95% CI:1.13–1.82 for one parent and OR=1.64, 95% CI:1.20–2.26 for both parents), MDD PRS was significantly associated with SA (OR=1.22 [95% CI:1.10–1.36]). In the second cohort, 204 (4.2%) of 4900 soldiers reported a lifetime history of SA. In a multivariable model that included personal [OR=3.82, 95% CI:2.77–5.26] and parental history of MDD [OR=1.42, 95% CI:0.996–2.03 for one parent and OR=2.21, 95% CI:1.33–3.69 for both parents) MDD PRS continued to be associated (at p = 0.0601) with SA (OR = 1.15 [95% CI:0.994–1.33]).

Conclusions: A soldier's PRS for MDD conveys information about likelihood of a lifetime SA beyond that conveyed by two predictors readily obtainable by interview: personal or parental history of MDD. Results remain to be extended to prospective prediction of incident SA. These findings portend a role for PRS in risk stratification for suicide attempts.

INTRODUCTION

Suicide is a serious societal and public health problem [Fazel and Runeson 2020]. In the United States, suicide is the 10th leading cause of death, and the 2nd leading cause of death for individuals between the ages of 10–34 [CDC 2018], and rates continue to increase [Hedegaard et al. 2018]. Predictions based on prior viral outbreaks and recent data suggest that suicide attempts (and, possibly, suicide deaths) will further increase as a result of the COVID-19 pandemic. Accordingly, whereas suicide has been on the radar of public health proponents for some time, its pervasiveness and impact on population health has been magnified of late.

Nowhere has this concern raised more alarms than in the United States military, where from 2014 to 2019, the suicide death rate for the Active Component increased from 20.4 to 25.9 suicides per 100,000 Service members [Defense 2020]. Despite a great deal of research into risk factors [Holliday et al. 2020] and substantial investments in suicide prevention [Curley et al. 2020; Stein et al. 2019], it remains uncertain why suicidality has trended higher. These observations have called for the development of better risk prediction models that can help target those individuals at highest risk [Kessler et al. 2020].

An emerging body of research has extended the search for suicide risk factors to genetic risk. Twin studies had initially set the stage for expecting to find specific genetic risk factors, providing heritability estimates of 30–55% [Tidemalm et al. 2011]. It is now clear that suicidal behaviors are genetically complex – as are most neuropsychiatric traits [Wendt et al. 2020] – and the evidence suggests that many common variants each of small effect contribute to risk (with the possibility of rare variants conferring greater risk) [Sokolowski and Wasserman 2020]. Epidemiological studies have taught us that risk factors for various aspects of self-harm (i.e., ideation, attempts, and deaths) are only partially overlapping

[Naifeh et al. 2020; Nock et al. 2013], and that a one-model-fits-all scenario is unlikely to be accurate. These lessons have filtered down to the genetic epidemiological study of self-harm where, increasingly, studies are each centered on one stage or type of self-harm (e.g., suicide ideation; suicide attempts; violent suicide attempts; suicide deaths).

Early genetic studies of suicidality, including our own genome-wide association study (GWAS) of suicide attempts in US Army soldiers [Stein et al. 2017], tended to be underpowered [Mirkovic et al. 2016]. More recent GWAS of suicide attempts, which have achieved much larger sample sizes due to data-sharing within and across consortia, have emphasized a genetic correlation between major depressive disorder (MDD) and suicide attempts [Levey et al. 2019; Mullins et al. 2019]. That is, genetic risk for depression is related to genetic risk for suicide attempts. Similar conclusions were reached from a recent GWAS of death by suicide, which found a polygenic association with MDD (and several other behavioral traits phenotypically linked with suicide deaths) [Docherty et al. 2020].

In the present study, we used data from two cohorts evaluated in the Army Study to Assess Risk and Resilience in Servicemembers (STARRS) [Naifeh et al. 2019] to determine the extent to which polygenic risk for MDD was associated with a history of suicide attempt (SA), over and above the robust risk associated with two depression-related characteristics that can be obtained without genetic data: personal history of MDD and parental history of MDD [Franklin et al. 2017; Ribeiro et al. 2018], asking the question: Do we get more (that could be applied clinically) from adding genetic data to what we could get from clinical observation alone? We reasoned that if personal and parental history accounted for most or all of the variance attributable to polygenic risk for MDD, then the former might serve as suitable proxies for the latter, which requires the collection of DNA and genotyping. On the other hand, if polygenic risk for MDD conveyed information about risk for SA that could not be obtained by knowledge of personal and parental history of MDD, then it might emerge as a useful, independent (or additive) SA risk marker.

METHODS

Subjects

Data come from two components of Army STARRS: the *New Soldier Study (*NSS*)* and the *Pre/Post Deployment Study (*PPDS*).* Detailed information about the design and conduct of STARRS is available in a separate report [Ursano et al. 2014]. Soldiers from the respective studies described below are nonoverlapping as confirmed by genetic analysis.

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. Of 39,784 NSS respondents who completed the Self-Administered Questionnaire (SAQ), 33,088 (83.2%) provided blood samples. Funding constraints led us to genotype a subset of respondents that would be optimally informative for the aims of STARRS: All cases of reported lifetime suicide attempt (SA) and PTSD were genotyped, as were a set of controls stratum-matched on sex, service type (Regular Army vs. Guard/Reserve), and childhood adversity quartile (detailed

description available on request from the authors). The NSS analyses described herein include 6,573 soldiers of European ancestry with available survey and genotype data (see below).

Pre/Post Deployment Study (PPDS).

The PPDS collected baseline data (also using a version of the SAQ) 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. The PPDS analyses described herein include 4,900 soldiers of European ancestry with available survey and genotype data (see below).

Measures

The SAQ surveyed socio-demographic characteristics, lifetime and past-30-day mental disorders, and an array of potential risk and resilience factors.

Suicidality Assessment.—Suicidal behaviors were assessed using an adaptation of the Columbia Suicidal Severity Rating Scale (C-SSRS) [Posner et al. 2011]. Pertinent to the data presented here, all respondents were asked if they had a history of suicide attempt (*"Did you ever make a suicide attempt [i.e., purposefully hurt yourself with at least some intention to die]?"*).

This information was available at baseline for NSS and PPDS, and at approximately 6- and 9-months post index deployment for PPDS. It was also available at later dates for those NSS and PPDS soldiers who subsequently took part in a 6- to 8-year follow-up survey referred to as STARRS-LS (STARRS Longitudinal Survey), for which data collection began 12 September 2016 and ended 10 April 2018. The STARRS-LS survey was conducted using a mixed-mode design, with participants given the option of completing the interview as a self-administered survey on the web, or with an interviewer over the telephone. This self-report information on suicidality was complemented by access to Army health records where suicide attempt(s) were recorded if medical attention was sought. For the analyses presented here, cases are soldiers with a lifetime history of SA (from either self-report or Army health records) and controls are those individuals with no lifetime history of SA.

Personal Lifetime History of Major Depressive Disorder.—The Army STARRS survey included a module, based on the Composite International Diagnostic Interview Screening Scales (CIDI-SC), for the ascertainment of a personal (lifetime) history of MDD [Kessler et al. 2013]. This was determined at the baseline assessment for either NSS or PPDS.

Parental History of Major Depressive Disorder.—The Army STARRS surveys queried parental history of MDD separately for the respondent's biological mother and father. The survey item *("Did any of them ever have times lasting two weeks or longer when*

they were so depressed they couldn't concentrate, felt worthless, or felt their life was not worth living?") was derived from the Family History Screen [Weissman et al. 2000].

Genetic Data Collection and Procedures

Samples were genotyped using either the Illumina OmniExpress + Exome array with additional custom content or 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 procedures to obtain the genotype data for population assignment 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 $\geq$ 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).

Population (ancestry) assignment was conducted using standard methods (see [Stein et al. 2017] for details).

Statistical Analysis

Polygenic Risk Scores (PRS).—PRS analyses for the SA phenotype were conducted using PRS-CS-auto, a method that uses a Bayesian regression framework and places a continuous shrinkage prior on the effects sizes of SNPs in the discovery GWAS summary statistics [Ge et al. 2019]. PLINK 2.0 [Chang et al. 2015] was used to weight all SNPs by their effect sizes calculated using PRS-CS-auto and sum all SNPs into PRS for each individual in the target cohort. PRS analyses were conducted in the European ancestry subsamples only because of the unavailability of reference GWAS data for other populations [Choi et al. 2020; Peterson et al. 2019]. PGC-MDD summary statistics [Howard et al. 2019] (N = 807,553; 246,363 cases, 561,190 controls) were used as the discovery GWAS; 1000 Genomes European was used as the LD reference panel. PRS were standardized within each study (NSS and PPDS) and entered into univariate or multivariable logistic models, controlling for 10 ancestral principal components, age, tranche (for NSS, which had been genotyped in two tranches) and sex. Odds ratios and confidence intervals are provided for these analyses, which build from univariate to multivariable and are therefore not independent; multiple testing correction was, accordingly, not applied.

RESULTS

Findings in NSS

The NSS sample consisted of 417 lifetime SA cases (6.3%) and 6156 controls with no history of lifetime SA. The sample was 15% female. Mean age of the sample was 20.8 (sd 3.3) years; median = 20 years, interquartile range: 19–22 years. Lifetime history of MDD was positive in 1086 (17.0% of) soldiers; 1532 (23.3%) and 575 (8.8%) reported a family history for one or both parents, respectively (Table 1).

In univariate analyses, the MDD PRS was significantly associated with lifetime history of SA (OR = 1.29 [95% CI: 1.16–1.43]). MDD PRS continued to be significantly associated with SA (OR = 1.23 [95% CI: 1.11–1.37) in a multivariable model that included personal history of MDD (OR = 4.01 [95% CI: 3.24–4.97]); there was no significant interaction between these two variables. Similarly, MDD PRS was significantly associated with SA (OR = 1.27 [95% CI: 1.15–1.41) in a multivariable model that included parental history of MDD (OR = 1.57 [95% CI: 1.24–1.98] for one parent and OR = 2.00 [95% CI: 1.47–2.73] for both parents).

In a multivariable model that included all the aforementioned predictors (personal history of MDD [OR = 3.83, 95% CI: 3.09–4.75]; parental history of MDD [OR = 1.43, 95% CI: 1.13–1.82 for one parent and OR = 1.64, 95% CI 1.20–2.26 for both parents) MDD PRS continued to be significantly associated with SA (OR = 1.22 [95% CI: 1.10–1.36] (Table 2a).

Replication in PPDS—The PPDS sample consisted of 204 lifetime SA cases (4.2%) and 4696 controls with no history of lifetime SA. The sample was 4% female, reflecting the overwhelming male majority being deployed to combat at the time of the survey. Mean age of the sample was 25.9 (sd 5.9) years; median = 24 years, interquartile range: 21–29 years. Lifetime history of MDD was positive in 551 (11.2% of) soldiers; 764 (15.6%) and 194 (4.0%) reported a family history for one or both parents, respectively (Table 1).

In univariate analyses, the MDD PRS was significantly associated with lifetime history of SA (OR = 1.18 [95% CI: 1.03–1.36]). MDD PRS continued to be associated (at p = 0.0533) with SA (OR = 1.15 [95% CI: 0.998–1.33) in a multivariable model that included personal history of MDD (OR = 4.32 [95% CI: 3.17–5.88]); there was no significant interaction between these two variables. Similarly, MDD PRS was significantly associated with SA (OR = 1.17 [95% CI: 1.02–1.35) in a multivariable model that included parental history of MDD (OR = 1.79 [95% CI: 1.27–2.53] for one parent and OR = 3.18 [95% CI: 1.95–5.18] for both parents).

In a multivariable model that included all the aforementioned predictors (personal history of MDD [OR = 3.82, 95% CI: 2.77–5.26]; parental history of MDD [OR = 1.42, 95% CI: 0.996–2.03 for one parent and OR = 2.21, 95% CI 1.33–3.69 for both parents) MDD PRS continued to be associated (at p = 0.0601) with SA (OR = 1.15 [95% CI: 0.994–1.33] (Table 2b).

DISCUSSION

Recent studies have shown that genetic liability for major depressive disorder (MDD) is associated with risk for SA [Levey et al. 2019; Mullins et al. 2019; Mullins et al. 2014; Ruderfer et al. 2020] as well as for suicide death [Docherty et al. 2020]. What has not, to the best of our knowledge, been shown is the extent to which genomic information about MDD risk – conveyed through polygenic risk scores (PRS) – is associated with SA risk above and beyond other more readily collected sources of information about MDD risk such as personal and parental history of MDD.

In this study of United States Army soldiers, we found polygenic risk for major depressive disorder (MDD) was associated with lifetime risk of suicide attempt (SA) as determined by a combination of self-report and Army medical records. Importantly, we were able to show that MDD PRS added to the predictive utility of two readily obtainable self-report parameters of SA risk, personal (lifetime) and family history of MDD. Whereas it might have been expected that there would be a higher MDD PRS in those with a positive family history of MDD [Andlauer et al. 2021], it is noteworthy that MDD PRS added to the explanatory power of that self-report parameter alone. The same is true of personal history of MDD, on which MDD PRS is trained.

Strengths of the study are the relatively large sample sizes, the systematic ascertainment of SA through surveys and access to health records, and the ability to test for replication of findings across two cohorts. A weakness is the possibility of incomplete ascertainment (e.g., if soldiers who left the Army were not part of STARRS-LS, and they attempted suicide after leaving the Army, they would be misclassified as controls), which would have biased findings toward the null. Another potential weakness is that reports of SA by self-report and health record-reporting were not infrequently discordant, leaving open the possibility that additional reporting biases may have been operating. An additional potential shortcoming is that soldiers' reporting of parental history may be inaccurate. Another limitation is that the study was not able to test if MDD PRS would predict *new-onset* SA among soldiers who did not report SA at baseline; the number of new-onset cases was insufficient to provide sufficient statistical power for that analysis. Nevertheless, it will be crucial to demonstrate, in future prospective studies, whether MDD (or other) PRS offer predictive value in this regard. Lastly, our analyses focused solely on individuals of European ancestry [Peterson et al. 2019], given the known limitations of extending PRS from European to other ancestral groups. New approaches that combine family history and PRS data hold promise as a solution to this limitation [Hujoel et al. 2021], and could be applied to this and other samples in the future.

Recent work from our group has shown that parental history of suicide attempt is associated with increased risk of pre-enlistment suicide attempt among new soldiers in the US Army [Wang et al. 2021]. Twin and other genetically informative studies suggest that SA is moderately (17%) heritable [Fu et al. 2002], and that parental psychiatric illness explains almost half of the genetic transmission of SA [Kendler et al. 2020]. The largest GWAS of SA to date has found a SNP-based heritability of approximately 7% [Mullins et al. 2020]. As genomic studies of suicide attempts increase in size and power, we expect that

PRS for SA will become available and offer predictive utility over and above personal and family history, and perhaps even other sociodemographic and life (and combat) stress measures that frequently enter into SA predictive models [Kessler et al. 2020]. In the interim, consideration could be given to using available PRS, such as the MDD PRS used here (for which future iterations will no doubt become more powerful), in instances where GWAS data are available. Although we have shown this additional information to be useful in this specific context, much work needs to be done to demonstrate the utility of PRS outside of the military setting and, importantly, in studies that use prospective longitudinal designs to determine if PRS can contribute to the prediction of new (or recurrent) suicide attempts.

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Table 1:

Parental History of Major Depression

	Control	Case	Total
New Soldier Study			
Neither	4235 (68.8%)	231 (55.4%)	4466 (67.9%)
One	1405 (22.8%)	127 (30.5%)	1532 (23.3%)
Both	516 (8.4%)	59 (14.2%)	575 (8.8%)
Total	*6156 (100.0%)*	*417 (100.0%)*	*6573 (100%)*
Pre-Post Deployment Study			
Neither	3806 (81.1%)	136 (66.7%)	3942 (80.5%)
One	717 (15.3%)	47 (23.0%)	764 (15.6%)
Both	173 (3.7%)	21 (10.3%)	194 (4.0%)
Total	*4696 (100.0%)*	*204 (100.0%)*	*4900 (100.0%)*

Table 2a.

Multivariable model for lifetime suicide attempt in New Soldier Study (NSS)

Predictor	Odds Ratio (OR)	OR 95% CI	p-value
Lifetime Major Depression	3.83	3.09–4.75	<0.0001
One parent with major depression	1.43	1.13–1.82	0.0031
Both parents with major depression	1.64	1.20–2.26	0.0021
Major depression polygenic risk score	1.22	1.10–1.36	0.0002

Table 2b.

Multivariable model for prediction of lifetime suicide attempt in pre-post deployment study (PPDS)

Predictor	Odds Ratio (OR)	OR 95% CI	p-value
Lifetime Major Depression	3.82	2.77–5.26	<0.0001
One parent with major depression	1.42	0.996–2.03	0.0525
Both parents with major depression	2.21	1.33–3.69	0.0023
Major depression polygenic risk score	1.15	0.994–1.33	0.0601