Psychological Medicine

cambridge.org/psm

Original Article

Cite this article: Nichter B *et al* (2023). Genetic liability to suicidal thoughts and behaviors and risk of suicide attempt in US military veterans: moderating effects of cumulative trauma burden. *Psychological Medicine* **53**, 6325–6333. https://doi.org/10.1017/S0033291722003646

Received: 23 May 2022
Revised: 28 October 2022
Accepted: 4 November 2022
First published online: 29 November 2022

Key words:
Genetics; inflammation; military; polygenic risk; suicide attempt; trauma; veterans

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Genetic liability to suicidal thoughts and behaviors and risk of suicide attempt in US military veterans: moderating effects of cumulative trauma burden

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Abstract

Background. Little is known about environmental factors that may influence associations between genetic liability to suicidality and suicidal behavior.

Methods. This study examined whether a suicidality polygenic risk score (PRS) derived from a large genome-wide association study ($N = 122{,}935$) was associated with suicide attempts in a population-based sample of European-American US military veterans ($N = 1664$; 92.5% male), and whether cumulative lifetime trauma exposure moderated this association.

Results. Eighty-five veterans (weighted 6.3%) reported a history of suicide attempt. After adjusting for sociodemographic and psychiatric characteristics, suicidality PRS was associated with lifetime suicide attempt (odds ratio 2.65; 95% CI 1.37–5.11). A significant suicidality PRS-by-trauma exposure interaction emerged, such that veterans with higher levels of suicidality PRS and greater trauma burden had the highest probability of lifetime suicide attempt (16.6%), whereas the probability of attempts was substantially lower among those with high suicidality PRS and low trauma exposure (1.4%). The PRS-by-trauma interaction effect was enriched for genes implicated in cellular and developmental processes, and nervous system development, with variants annotated to the *DAB2* and *SPNS2* genes, which are implicated in inflammatory processes. Drug repurposing analyses revealed upregulation of suicide gene-sets in the context of medrysone, a drug targeting chronic inflammation, and clofibrate, a triacylglyceride level lowering agent.

Conclusion. Results suggest that genetic liability to suicidality is associated with increased risk of suicide attempt among veterans, particularly in the presence of high levels of cumulative trauma exposure. Additional research is warranted to investigate whether incorporation of genomic information may improve suicide prediction models.

Introduction

The number and rate of suicide deaths in the US has risen substantially over the past two decades. Recent national epidemiologic data indicate that from 2000 to 2019, there was a 34% increase in the age-adjusted number of suicide deaths in the general US population (Centers for Disease Control and Prevention, 2021). Suicide represents a leading cause of death in the US as well as a preventable public health problem. While suicide has increased nationwide during recent years, one subpopulation that remains at disproportionately elevated risk is US military veterans (Nichter et al., 2021b), who die by suicide at considerably higher rates relative to civilians (United States Department of Veterans Affairs, 2020). Indeed, after adjusting for age and sex differences, veterans are approximately 52% more likely to die by suicide relative to non-veteran US adults (United States Department of Veterans Affairs, 2020). Given the substantial toll that suicide has on communities, families, and society at large, there have been recent calls to better understand the genetic, sociodemographic, and psychosocial risk factors that place veterans and civilians at risk for suicide (Bryan & Rozek, 2018). In light of data suggesting that a history of non-fatal suicide attempt is the strongest risk factor for suicide mortality (World Health Organization, 2014), there has been particular

interest in broadening current knowledge about the antecedents of this behavior to inform suicide prevention and intervention efforts (Nock et al., 2018).

Genetics play an important role in the manifestation of suicide attempts (DiBlasi, Kang, & Docherty, 2021). Twin studies indicate that heritability estimates for suicide attempt range from 17% to 55% (Fu et al., 2002; Pedersen & Fiske, 2010; Voracek & Loibl, 2007). Furthermore, a recent genome-wide association study (GWAS) of suicide attempts yielded evidence for single nucleotide polymorphism (SNP)-based heritability of approximately 7% (Mullins et al., 2019). While earlier genetic studies focused on identifying specific candidate genes associated with suicidal thoughts and behavior (e.g. *5-HTTLPR*; Gibb, McGeary, Beevers, & Miller, 2006), it has become increasingly clear that suicidal behaviors are genetically complex and highly polygenic (Stein et al., 2021a, 2021b). Indeed, a recent study characterized the polygenic architecture of suicidality spectrum in 122 935 participants from the United Kingdom (UK) Biobank cohort (Strawbridge et al., 2019). This study found evidence for a novel broadly-defined suicidality PRS including suicidal and self-harm thoughts (e.g. 'thoughts that life was not worth living', 'contemplated self-harm or suicide') as well as behavior (e.g. 'acts of deliberate self-harm' and 'attempted suicide'). Such findings underscore the utility of polygenic risk scores (PRS) as a method to estimate an individual's genetic liability for suicidality.

A notable limitation in the existing suicide genetics literature is that few studies have examined whether environmental factors may moderate these effects. Exposure to traumatic experiences, for example, likely represents one of the most extreme forms of environmental stressor that has been shown to increase risk for multiple forms of psychopathology as well as suicidality (Hughes et al., 2017; Nichter, Hill, Norman, Haller, & Pietrzak, 2020a; Nichter, Norman, Haller, & Pietrzak, 2020b). Thus, it is plausible that greater cumulative exposure to traumatic life events may potentiate polygenic risk for suicidality and elevate odds of suicide attempt. Indeed, recent evidence suggests that genetic susceptibility for different forms of psychopathology may interact with traumatic stress to increase suicidality risk (Wendt et al., 2021; Wilcox et al., 2017). This area of research may be especially relevant to examine among military veterans, given that they represent a subgroup who report high levels of childhood and combat-related trauma relative to civilians (Afifi et al., 2016). To date, however, no known study has examined whether suicidality polygenic risk is associated with elevated risk for suicide attempts among veterans, or whether exposure to traumatic stress may potentiate these genetic effects.

To address the aforementioned gaps in the literature, we analyzed data from a population-based study of US European-American (EA) veterans from the National Health and Resilience in Veterans Study (NHRVS) to evaluate the following four aims: (a) examine the association between PRS derived from a large-scale GWAS (Strawbridge et al., 2019) of a broad spectrum of suicidal behaviors (referred to hereinafter as 'suicidality PRS'; $N = 122\,935$) and lifetime suicide attempt among veterans; (b) investigate whether cumulative trauma exposure moderates the association between suicidality PRS and lifetime suicide attempt; (c) conduct a gene-enrichment analysis and a multivariate gene-by-environment genome-wide interaction study (GEWIS) to identify possible biological mechanisms driving any observed associations; and (d) perform a drug repositioning analysis to identify existing drugs that may be repurposed for treating this behavior. Based on prior work (Na et al., 2021; Nichter et al., 2020a), we hypothesized that higher levels of suicidality PRS would show stronger associations with suicide attempt, and that lifetime trauma exposure would moderate these effects, such that individuals with high suicidality PRS and high trauma exposure would evidence the highest probability of lifetime suicide attempt.

Methods and materials

Participants

Data were drawn from 1664 EA veterans who participated in the NHRVS, a population-based study of US military veterans. The sampling methodology of the NHRVS has been described previously (Nichter et al., 2021a). Briefly, the NHRVS sample was drawn from KnowledgePanel®, a research panel of more than 50 000 households maintained by Ipsos, Inc. KnowledgePanel® is a probability-based, online, non-volunteer access survey panel of a nationally representative sample of US adults that covers approximately 98% of US households. Veterans completed a web-based survey and provided a saliva sample for genotyping. Ancestry and relatedness were verified using the provided genetic information. The average age of participants was 63.2 years (s.d. = 14.2: range 22–93); the majority were male (92.5%) and 31.4% were combat veterans. To permit generalizability of study results to the entire population of US veterans, Ipsos statisticians computed post-stratification weights using the benchmark distributions of sociodemographic characteristics of US military veterans from the most recent Current Veteran Population Supplemental Survey of the US Census Bureau's American Community Survey. The study followed the Strengthening the Reporting of Genetic Association Studies (STREGA) reporting guidelines. All participants provided informed consent and the Human Subjects Committee of the VA Connecticut Healthcare System approved the study.

Assessments

Suicide attempt

Affirmative endorsement of the dichotomous item, 'Have you ever tried to kill yourself?', with 'yes' indicative of a lifetime suicide attempt.

Trauma exposure

The Trauma History Screen (THS; Carlson et al., 2011) was used to assess cumulative exposure to the lifetime occurrence of 14 potentially traumatic events; the NHRVS additionally assessed exposure to life-threatening illness or injury. The sum of potentially traumatic events endorsed, ranging from 0 to 15, was used as an index of lifetime cumulative trauma burden.

Combat veteran status

Combat veteran status was assessed with the following question: 'Did you ever serve in a combat or war zone?'

Lifetime depression/PTSD. Probable lifetime major depressive disorder (MDD) was assessed using a modified self-report version of the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998). Probable lifetime PTSD was assessed using a lifetime version of the PTSD Checklist-Specific Stressor version (Weathers, Litz, Huska, & Keane, 1994), which assessed PTSD symptoms related to veterans' 'worst' event on the THS; scores $\geqslant 50$ were indicative of a positive screen. Veterans with

https://doi.org/10.1017/S0033291722003646 Published online by Cambridge University Press

lifetime PTSD or MDD were grouped given high diagnostic overlap among these disorders and because these disorders frequently co-occur among US veterans (Nichter, Norman, Haller, & Pietrzak, 2019).

Lifetime alcohol/drug use disorder. Probable lifetime alcohol use disorder (AUD) and drug use disorder (DUD) was assessed using a modified self-report version of the MINI (Sheehan et al., 1998). The MINI has been found to have comparably high validity and reliability to longer psychiatric interviews such as the Composite International Diagnostic Interview (Lecrubier et al., 1997). Veterans with lifetime AUD or DUD were combined given the substantial comorbidity between these variables in the NHRVS (Fuehrlein et al., 2016).

DNA extraction, genotyping, quality control, and imputation

DNA was extracted from saliva samples collected with Oragene DNA (OG-250) kits. Samples were genotyped on the Illumina (San Diego, CA, USA) PsychChip microarray at Yale. After quality control, to account for population stratification of non-related EA individuals, principal component (PC) analysis with the first 10 PCs was performed using Eigensoft (Price et al., 2006). Genotype imputation was conducted using SHAPEIT (Howie, Donnelly, & Marchini, 2009) for pre-phasing and IMPUTE (1000 Genomes Project Consortium, 2015) for imputation. The 1000 Genomes Project Phase 3 was used as the reference panel. After imputation, we retained 6 724 271 high-quality markers with imputed genotype probability >0.8, MAF>0.01, and SNP missingness <0.01. These variants were used for the PRS analysis.

Data analysis

Polygenic risk scoring

The PRSice-2 software was used to calculate PRS (Choi & O'Reilly, 2019). PRS approaches may have different accuracy in modeling polygenic risk of psychiatric traits (Ni et al., 2021). In the present study, we selected the clumping-thresholding method as it allows to follow up the PRS analysis with pathway enrichment and drug repositioning analyses. A suicidality GWAS performed in 129 335 participants of European ancestry from the UK Biobank was used as the base dataset (Strawbridge et al., 2019). In this previous study, the suicidality spectrum was defined with 'no suicidality', 'thoughts that life was not worth living', 'ever contemplated self-harm or suicide', 'act of deliberate self-harm not including suicide in the past', and 'attempted suicide in the past'. The NHRVS imputed dataset was used as the target for the PRS analysis. The two datasets included 5 372 255 shared variants. An LD cut-off of $R^2 = 0.3$ within a 500 kb window was used to calculate the PRS while excluding the major histocompatibility complex region of the genome due to its complex LD structure. Multiple p value thresholds were considered for SNP inclusion (5×10^{-8}, 10^{-7}, 10^{-6}, 10^{-5}, 10^{-4}, 0.001, 0.05, 0.3, 0.5, 1). PRS generated considering a PT = 5×10^{-8} showed the strongest association with suicide attempt in the NHRVS cohort and it was considered for the subsequent analyses.

PRS and PRS-by-moderator analysis

Suicidality PRS was not associated with cumulative trauma burden, combat veteran status, lifetime MDD/PTSD, or lifetime AUD/DUD (all r's < 0.05, all p's > 0.05), thus reducing the potential confounding due to PRS-by-environment correlations. A multivariable binary logistic regression analysis was conducted to examine associations between suicidality PRS, cumulative trauma exposure, and their interaction in relation to lifetime suicide attempt. These analyses were adjusted for age, sex, combat veteran status, lifetime MDD/PTSD, lifetime AUD/DUD, and the top 10 within-ancestry PCs.

Functional annotation

Nominally significant results ($p < 0.05$) from the multivariate gene–environment interaction analysis were mapped to genes using SNP Nexus (Chelala, Khan, & Lemoine, 2009). This tool maps each variant using dbSNP identifiers with the closest gene based on the major gene annotation systems (e.g. Ensembl, NCBI RefSeq). The GRCh38 genome assembly was used for the reference panel.

Multivariate gene–environment interaction analysis

To investigate further the gene–environment interactions (G×E) underlying the role of traumatic events as moderators in the association between suicidality PRS and suicide attempt, we used the Structured Linear Mixed Model (StructLMM) method to identify loci that potentially interact with multiple environments (multivariate gene–environment interaction) (Moore et al., 2019). We tested whether variants contributing to suicidality PRS interacted with different types of lifetime traumatic events (online Supplementary Table S1). The information regarding suicide attempt was regressed on age, sex, combat exposure, lifetime MDD/PTSD, and lifetime AUD/DUD. Residuals were entered as outcomes into StrucLMM. We tested multivariate G×E interactions for 11 508 LD independent genetic variants (minor allele frequency >5%) previously associated with suicidality in the UK Biobank at $p < 0.05$ (Strawbridge et al., 2019). A Bonferroni multiple testing correction was applied to the G×E interaction analysis considering the number of variants tested ($N = 11\,508$; $p = 4.34 \times 10^{-6}$). As a post hoc analysis, the model with all environments and the reduced model with each environment removed were compared using marginal log likelihoods [log; Bayes factor (*BF*)] to detect which environments contributed most to the G×E effects. Specifically, a backward elimination based on *BF* was conducted to identify the independent environments driving the multivariate G×E detected.

Gene enrichment analyses

The 5509 genes annotated using SNP Nexus were submitted to PANTHER (Thomas et al., 2003) to test for enrichment of relevant biological processes, cellular components, and molecular functions. The p values adjusted by the conservative Bonferroni correction method were considered significant ($p < 3.18 \times 10^{-6}$). The redundant gene ontology (GO) terms were clumped using REVIGO (Supek, Bošnjak, Škunca, & Šmuc, 2011), which applies a clustering algorithm that relies on semantic similarity measures.

Drug repurposing analyses

The Gene2drug tool (Napolitano et al., 2018) was used for drug repurposing analysis. Gene2drug applies Pathway-Set Enrichment Analysis (PSEA), which uses gene sets to identify gene pathways that are up- or down-regulated by drugs. This tool converts gene expression profiles from Connectivity Map (Subramanian et al., 2017) to pathway expression profiles then ranks p values of their Kolmogorov–Smirnov statistics. An enrichment score (EScore) is assigned to each drug to indicate up- or

https://doi.org/10.1017/S0033291722003646 Published online by Cambridge University Press

Table 1. Sample characteristics by lifetime suicide attempt history

	No suicide attempt $n = 1579$ (weighted 93.7%) Weighted mean (s.d.) or No. (%)	Suicide attempt $n = 85$ (weighted 6.3%) Weighted mean (s.d.) or No. (%)	χ^2 or t	p value
Age	63.8 (13.9)	53.2 (14.3)	7.12	<0.001
Male sex	1451 (92.9)	65 (87.1)	3.39	0.065
Combat veteran	520 (31.0)	32 (37.2)	1.59	0.21
Lifetime traumas	3.1 (2.4)	5.7 (3.8)	9.83	<0.001
Lifetime MDD or PTSD	234 (14.4)	61 (74.5)	212.94	<0.001
Lifetime AUD or DUD	704 (44.8)	62 (77.4)	37.21	<0.001

AUD, alcohol use disorder; DUD, drug use disorder; MDD, major depressive disorder; PTSD, posttraumatic stress disorder; s.d., standard deviation.

down-regulation and its magnitude. All Bonferroni significant clumped GO terms were used as input for Gene2drug. Bonferroni significance threshold was defined considering the number of drugs tested ($N = 1309$; $p = 3.81 \times 10^{-5}$).

Results

Table 1 presents descriptive statistics of the sample. Eighty-five veterans (weighted 6.3%, 95% CI 5.1–7.6%) reported a history of suicide attempt. Veterans with a history of suicide attempt were more likely to be younger (53.2 ± 14.3 *v.* 63.8 ± 13.8, $p < 0.001$), reported more lifetime traumas (3.8% *v.* 2.4%, $p < 0.001$), and were more likely to screen positive for lifetime MDD/PTSD (74.5% *v.* 14.4%, $p < 0.001$) and AUD/DUD (77.4% *v.* 44.8%, $p < 0.001$).

As shown in Table 2, suicidality PRS, cumulative trauma exposure, lifetime MDD/PTSD and AUD/DUD were positively associated with lifetime suicide attempt, while age was negatively associated with this outcome. A significant interaction of suicidality PRS × cumulative trauma exposure was also observed (adjusted OR 1.11; 95% CI 1.01–1.22). Figure 1 shows the interaction between suicidality PRS and lifetime trauma exposure, which indicated that veterans in the highest tertiles of suicidality PRS and lifetime trauma exposure had the highest probability of lifetime suicide attempt (0.173). Interactions between suicidality PRS and other potential moderator variables, including lifetime MDD/PTSD, AUD/MDD, and combat veteran status, were not significant.

Multivariate gene–environment interaction analysis

Based on the PRS results, we analyzed multivariate G×E effects with respect to 11 508 LD independent genetic variants (minor allele frequency >0.5%) that reached a nominally significant association ($p < 0.05$) with respect to suicidality in the UK Biobank ($N = 122\,822$; Strawbridge et al., 2019). After false discovery correction (FDR $q < 0.05$), the multivariate G×E analysis revealed 25 variants with significant association with suicide attempt and significant multivariate G×E effects (online Supplementary Table S2). Among them, 11 loci showed large G×E interaction (*BF*>1) with at least one traumatic event. Three variants presented interactive effects with multiple types of traumatic events: rs12153248 ($p_a = 4.4 \times 10^{-5}$, $p_{int} = 2.07 \times 10^{-5}$; sudden abandonment *BF* = 4.35, sudden move/loss of possessions *BF* = 2.22; sudden death of loved one *BF* = 2.11); rs4656083 ($p_a = 5.11 \times 10^{-5}$, $p_{int} = 3.33 \times 10^{-5}$; natural disaster *BF* = 1.31, sudden abandonment *BF* = 1.29; child sexual abuse *BF* = 1.1); rs1351231 ($p_a = 7.56 \times 10^{-5}$, $p_{int} = 3.87 \times 10^{-5}$; sudden death of loved one *BF* = 2.24, life-threatening illness or injury *BF* = 1.43; natural disaster *BF* = 1.37). The rs12153248 and rs1351231 variants were annotated to the *DAB2* and *SPNS2* genes, respectively. The rs4656083 SNP is located in an intergenic region.

Table 2. Results of binary logistic regression analysis of suicidality PRS, lifetime trauma exposure, and their interaction in relation to lifetime suicide attempt

	Lifetime suicide attempt *v.* no attempt Adjusted OR[a] (95% CI)
Age	0.98 (0.97–0.99)
Male sex	0.64 (0.29–1.41)
Suicidality PRS	2.65 (1.37–5.11)
Combat veteran	0.96 (0.55–1.68)
Lifetime traumas	1.20 (1.10–1.31)
Lifetime MDD or PTSD	8.18 (4.62–14.49)
Lifetime AUD or DUD	2.59 (1.43–4.67)
Suicidality PRS × lifetime trauma exposure	1.11 (1.01–1.22)

95% CI, 95% confidence interval; AUD, alcohol use disorder; DUD, drug use disorder; MDD, major depressive disorder; OR, odds ratio; PRS, polygenic risk score (standardized); PTSD, posttraumatic stress disorder; s.d., standard deviation.
[a]Results are adjusted for top 10 within-ancestry principal components.

Gene set enrichment and drug repurposing analyses

GSEA was applied to detect overrepresented pathways for the 5509 genes identified with SNP Nexus (online Supplementary Table S3). After Bonferroni multiple correction testing, we identified 109 significant enrichments ($p < 3.18 \times 10^{-6}$) (online Supplementary Table S4). After clumping the redundant GO terms, 54 pathways (online Supplementary Table S4) were identified with >60% semantic uniqueness (i.e. the negative of average similarity of a term to all other terms) and <60% semantic dispensability (i.e. value reflecting the term's strong redundancy with respect to a chosen representative). The strongest enrichments included cellular process (GO:0009987; 1.11-fold enrichment, $p = 2.73 \times 10^{-25}$), developmental process (GO:0032502; 1.32-fold enrichment, $p = 4.57 \times 10^{-24}$), and nervous system development (GO0007399; 1.59-fold enrichment, $p = 1.15 \times 10^{-23}$).

https://doi.org/10.1017/S0033291722003646 Published online by Cambridge University Press

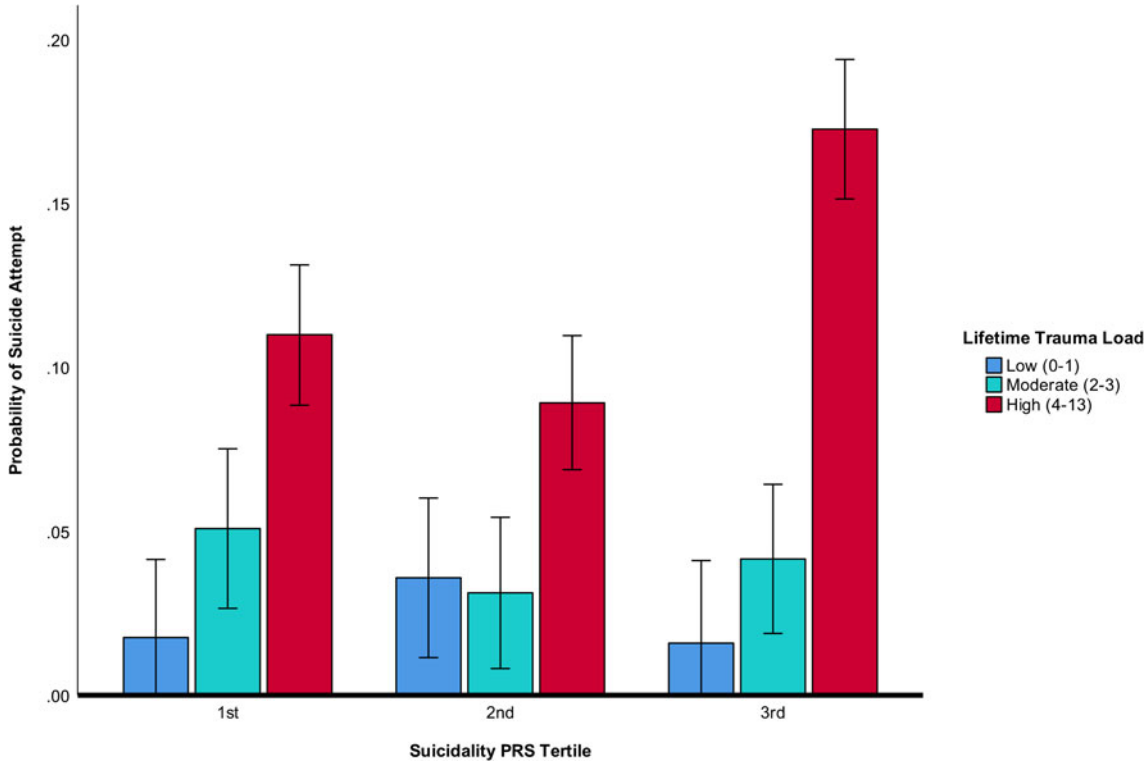

Fig. 1. Probability of lifetime suicide attempt as a function of suicidality PRS and cumulative lifetime trauma burden. *Note.* Error bars represent 95% confidence intervals.

For the drug repurposing analysis, we submitted GO terms significant in the GSEA analysis to Gene2drug (Napolitano et al., 2018). Among the drugs tested, two compounds survived Bonferroni multiple testing correction: medrysone, a synthetic glucocorticoid with anti-inflammatory properties ($p = 2.29 \times 10^{-5}$, EScore = 0.437); clofibrate, a triacylglyceride level lowering agent ($p = 3.38 \times 10^{-5}$, EScore = 0.430) (online Supplementary Table S6).

Discussion

Leveraging phenotypic and genetic data available from the NHRVS cohort, a nationally representative sample of US military veterans, we found that higher suicidality PRS in European Americans was associated with greater odds of lifetime suicide attempt. Specifically, results indicated that each standard deviation increase in suicidality PRS was associated with a more than 2.5-fold greater odds of suicide attempt, even after adjusting for sociodemographic and military characteristics, as well as lifetime PTSD, MDD, AUD, and DUD. These results are consistent with accumulating data, which suggest that the cumulative effects of numerous common genetic polymorphisms may contribute to individuals' propensity toward engaging in suicidal behavior (Mullins et al., 2019, 2022; Na et al., 2021). For example, our previous study (Na et al., 2021) found that suicidality PRS was associated with approximately fourfold greater odds of developing new-onset of suicidal ideation over a 7-year period, above and beyond sociodemographic characteristics and lifetime psychiatric history. The current study extends our prior analysis investigating suicidality PRS in relation to the interplay with cumulative trauma burden and suicide attempt in US veterans of European descent.

Consistent with our hypotheses, we found a significant PRS-by-trauma exposure interaction, such that veterans with higher levels of suicidality PRS and lifetime trauma exposure showed the highest probability of lifetime suicide attempt (Fig. 1). Among individuals with high suicidality PRS, the likelihood of suicide attempt was greatest among those with high levels of lifetime trauma exposure (16.6%). Conversely, the probability of suicide attempt was only 1.4% among those with high suicidality PRS and low trauma exposure. This finding suggests that exposure to traumatic events may potentiate the effects of genetic liability for suicidality and contribute to increased risk for suicide attempt. Although our study is the first, to our knowledge, to document the synergistic effects of polygenic risk for suicidality and lifetime trauma exposure, findings are broadly consistent with other recent research demonstrating interactive effects between polygenetic risk for mood disorders and trauma exposure with suicide-related outcomes (Stein et al., 2021a, 2021b). Collectively, the PRS-by-environment effects found in our study are consistent with the vulnerability-stress model of suicidal behavior (Nock et al., 2013), which posits that individuals possess genetic variants that heighten their vulnerability to environmental stressors, and that sets of genes can be activated by specific environmental adversities (i.e. trauma exposure), elevating risk for suicidality.

A notable contribution of the current study is the results obtained from our GEWIS to better understand how specific traumatic life events may interact with gene variants to modulate risk for suicide attempts. Among the 25 variants with significant association with suicide attempt and significant multivariate G×E effects, three variants were associated with different sets of traumatic events. This is in line with a previous study conducted in

https://doi.org/10.1017/S0033291722003646 Published online by Cambridge University Press

the UK Biobank where variants presented different profiles to timing (e.g. childhood *v.* adulthood) and types (emotional *v.* physical) of traumatic experiences (Wendt et al., 2021). Two risk loci were mapped to genic regions: rs12153248 mapped to *DAB2* and rs1351231 mapped to *SPNS2*. The *DAB2* gene encodes Disabled-2, a phosphoprotein with a possible role as a tumor suppressor. This protein binds to the GRB2 adaptor protein, which may modulate the Ras signaling pathway (Mok et al., 1994). *GRB2* was found to be a risk gene for schizophrenia (Sun et al., 2011), a psychiatric disorder that can be exacerbated by traumatic events (Popovic et al., 2019). In the present study, G×E with the *DAB2* rs12153248 variant showed interaction with sudden abandonment, sudden move/loss of possession, and sudden death of loved one to predict suicide attempt. Although relatively few cases of schizophrenia result from an identifiable, sudden traumatic event (McIntosh & Story, 2021), this form of psychopathology is often associated with suicide attempt (Popovic et al., 2019). This relationship suggests that the *DAB2* gene may play a role in suicidality risk and inter-individual susceptibility to traumatic events.

The *SPNS2* gene encodes a sphingosine 1-phosphate transporter, a secreted lipid relevant in cardiovascular, immunological, and neural development. *SPNS2* deficiency was previously associated with early-onset progressive hearing loss (Chen et al., 2014) and the protein plays several roles in immune response, among them lymphocyte exit from lymphoid organs to circulation (Baeyens & Schwab, 2020). Lymphocytes have been suggested as useful biomarkers in several psychiatric disorders and suicidal behaviors (Brundin, Erhardt, Bryleva, Achtyes, & Postolache, 2015; Kuballa, Nolte, Castoreno, & Xavier, 2012; Osimo et al., 2020; Pandey, 2013). Specifically, various pro-inflammatory cytokines have been identified as potentially important in understanding the pathophysiology of suicidal behavior (Pandey, 2013). Our data suggest that *SPNS2* may be associated with trauma-related suicidal behavior through inflammatory processes. Confirming this hypothesis, in the drug repurposing analysis, we found upregulation of suicide gene-sets in the context of medrysone, a drug used for chronic inflammation.

A previous study investigated electronic health records from medical claims for private health insurance, identifying several drugs associated with increased and decreased risk of suicidal events (Gibbons, Kwan, Lavigne, Wang, & Mann, 2019). None of the drugs reported in this investigation overlapped with the ones we identified in the current study. This is likely due to the different analytic design of the two studies. Indeed, while the results presented by Gibbons and colleagues are influenced by the comorbidities within the sample investigated and the prevalence of the drug prescriptions, our findings are influenced by the molecular targets known to be related to the drugs investigated. The different findings observed likely reflect the complexity of investigating suicidal behaviors.

Results from gene set enrichment analyses provide further insight into the possible biological basis of suicide attempts. Overrepresented pathways in the gene set enrichment analysis included cellular process, developmental process, and nervous system development. Other than lymphocytes, several other cells and cellular processes (e.g. platelets, leukocytes) have been implicated in the development of psychiatric disorders (Carballo, Akamnonu, & Oquendo, 2008). Developmental processes, such as neuronal development through Brain-derived neurotrophic factor have also suggested to play a role in the pathophysiology of suicide (Pandey, 2013). Additionally, lasting alterations in the hypothalamic–pituitary–adrenal axis and serotonergic and dopaminergic systems in early life are associated with suicidal behavior in adulthood (Carballo et al., 2008).

The results of this study should be interpreted in the context of several limitations. First, it is unclear from the current study to what extent polygenic risk and trauma exposure play a causal role in suicide attempts. Additional population-based, genetically-informed studies using techniques to strengthen causal inference (e.g. Mendelian randomization) are needed to better understand the nature of these relationships. Second, although a significant strength of this study was that it drew from a nationally representative sample of EA US veterans, results may not generalize to more racially/ethnically diverse veterans or non-veteran populations that may have different trauma histories. Although previous studies of multiple psychiatric disorders showed that genetic effects observed in predominantly-male cohorts are highly consistent with those identified in sample more equally representing males and females (Levey et al., 2020, 2021; Stein et al., 2021a, 2021b), we acknowledge that the difference between the sex distribution in base and target samples of our PRS analysis may have affected our statistical power. Third, emerging evidence suggests that the timing of trauma exposure may be an important variable to consider in understanding the impact of polygenic risk for psychopathology (Aas et al., 2021; Carballo et al., 2008), but timing was not assessed in this study; further research is needed to evaluate whether this may also apply to suicidal behaviors. Lastly, given the relatively limited sample size of the NHRVS cohort, it is possible that the effects detected in our study may be inflated due to the winner's course bias. Accordingly, further studies will be needed to replicate our results in an independent cohort.

Notwithstanding these limitations, results of this study have several important implications. From a research perspective, the finding that PRS scores for suicidality interacted with cumulative trauma exposure to elevate risk for suicide attempt suggests that future suicide research would benefit from incorporating genomic information to better understand how genetic and environmental factors may interact to heighten suicide risk, as well as to improve outcome prediction. Indeed, it is notable that suicidality PRS added to the explanatory power of the suicide attempt prediction model, above and beyond several of the strongest empirically validated risk factors, including lifetime MDD/PTSD/AUD (Nichter et al., 2021a; Nock et al., 2013). Moreover, results accord with a growing body of other evidence (Brundin et al., 2015) to suggest that genes associated with inflammatory processes (e.g. *DAB2*, *SPNS2*) may be associated with increased risk for suicide attempts, and therefore warrant further investigation.

Although the predictive clinical utility of the PRS investigated in the present study remains to be determined, our results suggest that considering PRS generated from more powerful genomic studies (e.g. whole-genome sequencing studies) in combination with other environmental factors (e.g. trauma history; Nichter et al., 2022) may potentially help inform risk stratification and clinical decision-making for suicidality in the future. Indeed, as highlighted in a recent review (Murray et al., 2021), genomic data needed to calculate PRS are inexpensive and easy to collect, and could help inform clinical decision-making in a similar way that clinicians currently use information recorded about family history of psychopathology to stratify patients at most risk and in need of a greater level of surveillance.

Finally, our drug repurposing analyses identified a molecular compound targeting inflammatory pathways, which preliminary

https://doi.org/10.1017/S0033291722003646 Published online by Cambridge University Press

results suggest could potentially be repurposed to treat suicidal behavior. However, our drug-repositioning approach is designed only to investigate drugs that could alter the expression profile (i.e. up- or down-regulation) of pathways associated with the phenotype of interest (suicide attempt in our study). Further studies are needed to clarify the potential consequences of these molecular changes. Indeed, there have been increasing calls in recent years for a better understanding of medications that may be helpful for reducing suicidal behavior both proximally and distally, particularly in light of rising rates of suicide in the United States over the past decade (Gibbons et al., 2019). Further research is additionally needed to examine the association between suicidality PRS and suicide-related outcomes in non-veteran EA and non-EA samples, as well as to identify biopsychosocial mechanisms linking this gene-by-environment interaction to the phenotypic expression of suicidal behaviors.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291722003646.

Acknowledgements. Preparation of this report was supported in part by the US Department of Veterans Affairs National Center for Posttraumatic Stress Disorder. The authors acknowledge Ann Marie Lacobelle and Christa Robinson from the Gelernter Laboratory for their assistance in sample processing. None of the funding sources had a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The authors thank the veterans who participated in this study. RP and BN had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses.

Financial support. Preparation of this report was supported in part by the Clinical Neurosciences Division of the US Department of Veterans Affairs National Center for Posttraumatic Stress Disorder. This funding source had no role in the design of this study, execution, analyses, interpretation of the data, or decision to submit the manuscript.

Conflict of interest. BN, DK, FD, JW, MG, PN, SN, and RHP have no conflicts of interest to declare. MH is a paid consultant for Spectrum Therapeutics. RP and JG are paid for their editorial work on the journal *Complex Psychiatry*. RP received a research grant from Alkermes. JK is a scientific advisor to Biohaven Pharmaceuticals, BioXcel Therapeutics, Inc., Cadent Therapeutics (Clinical Advisory Board), PsychoGenics, Inc., Stanley Center for Psychiatric research at the Broad Institute of MIT and Harvard, Lohocla Research Corporation. JK owns stock and/or stock options in Biohaven Pharmaceuticals, Sage Pharmaceuticals, Spring Care, Inc., BlackThorn Therapeutics, Inc., Terran Biosciences, Inc. JK reports income <$10 000 per year from: AstraZeneca Pharmaceuticals, Biogen, Idec, MA, Biomedisyn Corporation, Bionomics, Limited (Australia), Boehringer Ingelheim International, Concert Pharmaceuticals, Inc., Epiodyne, Inc., Heptares Therapeutics, Limited (UK), Janssen Research & Development, L.E.K. Consulting, Otsuka America Pharmaceutical, Inc., Perception Neuroscience Holdings, Inc. Spring Care, Inc., Sunovion Pharmaceuticals, Inc., Takeda Industries, Taisho Pharmaceutical Co., Ltd. JK reports income >$10 000 per year from Biological Psychiatry (Editor). JK received the drug, Saracatinib from AstraZeneca and Mavoglurant from Novartis for research related to NIAAA grant 'Center for Translational Neuroscience of Alcoholism' [CTNA-4] from AstraZeneca Pharmaceuticals. JK holds the following patents: (1) Seibyl JP, Krystal JH, Charney DS. Dopamine and noradrenergic reuptake inhibitors in treatment of schizophrenia. US Patent #:5447948. 5 September 1995; (2) Vladimir, Coric, Krystal, John H, Sanacora, Gerard – Glutamate Modulating Agents in the Treatment of Mental Disorders US Patent No. 8778979 B2 Patent Issue Date: 15 July 2014. US Patent Application No. 15/695164: Filing Date: 09/05/2017; (3) Charney D, Krystal JH, Manji H, Matthew S, Zarate C, – Intranasal Administration of Ketamine to Treat Depression United States Application No. 14/197767 filed on 5 March 2014; United States application or Patent Cooperation Treaty (PCT) International application No. 14/306382 filed on 17 June 2014; (4): Zarate, C, Charney, DS, Manji, HK, Mathew, Sanjay J, Krystal, JH, Department of Veterans Affairs 'Methods for Treating Suicidal Ideation', Patent Application No. 14/197.767 filed on 5 March 2014 by Yale University Office of Cooperative Research; (5) Arias A, Petrakis I, Krystal JH. – Composition and methods to treat addiction. Provisional Use Patent Application no. 61/973/961. 2 April 2014. Filed by Yale University Office of Cooperative Research.; (6) Chekroud, A., Gueorguieva, R., Krystal, J.H. 'Treatment Selection for Major Depressive Disorder' [filing date June 3, 2016, USPTO docket number Y0087.70116US00]. Provisional patent submission by Yale University; (7) Gihyun, Yoon, Petrakis I., Krystal J.H. – Compounds, Compositions and Methods for Treating or Preventing Depression and Other Diseases. U.S. Provisional Patent Application No. 62/444552, filed on January 10, 2017 by Yale University Office of Cooperative Research OCR 7088 US01; and (8) Abdallah, C., Krystal, J.H., Duman, R., Sanacora, G. Combination Therapy for Treating or Preventing Depression or Other Mood Diseases. U.S. Provisional Patent Application No. 62/719935 filed on 20 August 2018 by Yale University Office of Cooperative Research OCR 7451 US01.

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