# PSYCHIATRIC DISORDER IN VETERANS

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# PSYCHIATRIC DISORDER IN VETERANS

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EDITORIAL
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# Editorial: Psychiatric Disorder in Veterans

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**Keywords: veterans, mood disorders, PTSD, psychiatry, public policy, stress**

**Editorial on the Research Topic**

**Psychiatric Disorder in Veterans**

## INTRODUCTION

Mental health issues in Veterans of the Armed Forces have wide-ranging effects. Factors related to military service, especially from combat related deployments, include environmental exposures, stressors, and physical traumas and injuries, with potential to places service members at heightened risks for the development of neuropsychiatric disorders. There exists a great need to identify contributory factors, elucidate mechanisms, investigate treatments, and apply these findings in a multiple tiered approach, aimed at translating basic research findings to evidence-based applications in the clinic. To improve mental health outcomes for Veterans, public health interventions and supportive public policies are vital to ensure access to the most effective mental health services. This special issue represents a collection of original research articles and review articles from esteemed colleagues who have conducted scientific research highly focused on the common goals of addressing, understanding and improving the mental health of Veterans.

## PREVALENCE OF MENTAL HEALTH DISORDERS IN VETERANS

Mental health illness presents many challenges for society, and is of imminent importance within the U.S. Veteran population. Our military service men and women are placed under unique conditional stressors that have put veterans at higher risk of developing neuropsychiatric illness including depression, anxiety, and posttraumatic stress disorder (PTSD) (1). Understanding the contributory factors leading to a predisposition for the development of neuropsychiatric illness in this population is a challenging but critical component in developing effective therapeutics and interventions to treat mental health among veterans.

The insecurity, trauma, and pressure of warfare causes tremendous stress, which makes it an important focus of research efforts. Following Israeli Veterans from the battlefield, to their reintegration into civilian life, Solomon provides a meaningful review of systematic trauma research focusing on the psychopathological effects on Israeli veterans. Her work is distinct, as Israel and its inhabitants have lived through periods of intense war, making the country a natural stress laboratory with a unique opportunity to study a war-like environment (2) and test potential prevention and treatment solutions.



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## CONTRIBUTING FACTORS

Various military service-related factors including stress, physical trauma, and environmental exposures have been investigated for their contributory roles in the development of mental health pathologies in Veterans. This nexus of predisposing factors is evident in the pathogenesis of Gulf War Illnesses (GWI). GWI is a chronic, multi-symptom disorder affecting approximately one third of all troops deployed to the Persian Gulf during the Gulf War (1990-91). Neuropsychiatric effects include memory dysfunction, PTSD, depression, and anxiety. The similarity of neuroinflammatory changes observed in both neuropsychiatric conditions and GWI is at the forefront of Trageser et al. review. As there is currently no approved treatment for GWI, these commonalities may be leveraged as a target for therapeutic interventions.

Veterans are also at a heightened risk of PTSD compared to the general population; Veterans deployed during Operation Enduring Freedom and Operation Iraqi Freedom exhibited a prevalence of 15.8%, compared to a 6.1% lifetime prevalence in the general population (2, 3). Toward investigating PTSD in veterans, Ypsilanti et al. examined the associations of self-disgust, loneliness, and mental health issues in Veterans with PTSD. In this study, the loneliness and anxiety symptoms of Veterans with PTSD is shown to be mediated by self-disgust measures. These findings have wide-ranging impacts for targeting treatments for the improvement of these symptoms.

Various neuropsychiatric disorders place individuals at risk for the development of Alzheimer's disease and other dementias (4). With the increased incidence of mental health issues in Veterans, in addition to other heightened risk factors, this link represents a vital area of research. Zhu and Sano describe these risk factors and approaches to prevent the development of Alzheimer's disease in the Veteran population.

## MOVING FORWARD

To address the wide-reaching impacts of mental health disorders in the Veteran population, innovative, and evidence-based, treatment strategies and public policies should be employed. Alternative and innovative interventions interventions are essential in the treatment of psychiatric disorders in Veterans. Rodriguez et al. explores the utilization of a PTSD Service Dog intervention in Veterans afflicted with PTSD. Service dogs trained in a variety of therapy tasks were successfully able to attenuate many symptoms of PTSD, including those of hypervigilance and anxiety (5).

Toward identifying key factors that are integral for improving the mental health of Veterans, Fogle et al. has provided an invaluable review of all studies conducted by the National Health and Resilience in Veterans Study (NHRVS). To reduce the risks associated with mental disorders, it is essential to promote community integration and social engagement, and help individuals develop positive protective psychosocial characteristics.

Federal funding for research that is specific to improving mental health care for Veterans is essential. Activities such as collaborations across the major funders, the Department of Veterans Affairs (VA), Department of Defense and National Institutes of Health have been highly fruitful in identifying effective solutions. One of the major research programs, the Congressionally Directed Medical Research Program (CDMRP), is described by Lane et al. as highly collaborative and focused on making research awards tailored to areas of greatest need for active duty military and Veterans.

As described in Carroll et al. suicide prevention is the number one clinical priority of the VA. A multi-tiered approach aimed at addressing suicidality in Veterans both in the clinic and from community-based interventions is essential to prevent suicide in Veterans, as well as the general population. The VA's suicide prevention program has served as a model for others.

## CONCLUSION

Mental health issues in the Veteran population represent a significant social, economic, and public health burden, with wide ranging impacts. Research aimed at elucidating the mechanisms, the development of interventions, and application of public health initiatives and public policies targeting mental health issues in Veterans is vital. These articles featured by our colleagues represent novel strategies aimed toward achieving the goals of advancing evidence-based prevention and treatment solutions.

## AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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ORIGINAL RESEARCH
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# Defining the PTSD Service Dog Intervention: Perceived Importance, Usage, and Symptom Specificity of Psychiatric Service Dogs for Military Veterans

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Research suggests that psychiatric service dogs may be an effective complementary treatment option for military veterans with posttraumatic stress disorder (PTSD). Although this practice continues to increase in popularity and research has reached the rigor of clinical trials, the components of the PTSD service dog intervention remain largely undefined. This research aimed to (1) quantify the importance, usage, and PTSD symptom specificity of service dog trained and untrained behaviors, (2) explore how PTSD severity, time since receiving the service dog, and the veteran-dog relationship relate to outcomes, and (3) compare expectations of veterans on the waitlist to experiences of veterans with service dogs. In a cross-sectional design, 217 post-9/11 military veterans with PTSD were recruited from a national service dog provider, including $n$ = 134 with a service dog and $n$ = 83 on the waitlist. Results showed that the service dog's trained tasks of calming and interrupting anxiety were perceived as the most important for veterans' PTSD, the most frequently used in a typical day, and as helping the most PTSD symptoms. Trained tasks were most helpful to the PTSD symptoms of hypervigilance and intrusion, and least helpful toward the symptoms of amnesia and risk-taking. Although all trained tasks were helpful toward PTSD symptoms, veterans rated the service dog's untrained behaviors on average as more important for their PTSD. After controlling for covariates, there was no relationship between a veteran's PTSD severity and perceived importance or frequency of task use. However, veterans who reported feeling closer to their service dogs reported using trained tasks more often, and veterans who had their service dogs for longer reported using trained tasks less often. Finally, veterans on the waitlist reported higher expectations regarding task use and importance than described by veterans with a service dog. In conclusion, findings

describe the core components of the PTSD service dog intervention by quantifying the use and value of trained and untrained dog behaviors. Overall, this study helps explain the PTSD service dog's clinically relevant value while contributing to the scientific understanding of this emerging practice.

**Keywords: PTSD service dogs, psychiatric service dogs, military veterans, PTSD, animal-assisted intervention, human–animal interaction, human–animal bond**

## INTRODUCTION

Of the roughly 2.7 million United States military personnel deployed to Iraq and Afghanistan post-9/11, up to 23% return with diagnostic symptoms of posttraumatic stress disorder (PTSD; Fulton et al., 2015). PTSD is a pervasive mental health condition that can occur after exposure to a traumatic event characterized by avoidance, re-experiencing, negative alterations in cognition and mood, and hyperarousal (American Psychiatric Association, 2013). Several evidence-based treatment options for PTSD exist, including cognitive behavioral therapy, prolonged exposure therapy, and pharmacotherapy (Foa et al., 2008). However, treatment dropout rates are often high among military veterans, and many veterans will retain their PTSD diagnosis despite treatment completion (Resick et al., 2015; Steenkamp et al., 2015). To meet the needs of military veterans with pervasive PTSD symptoms, many complementary and alternative treatments and practices have emerged to supplement evidence-based care (McPherson and Schwenka, 2004).

One increasingly popular integrative treatment option for PTSD is the provision of a specially trained psychiatric service dog. Psychiatric service dogs are a form of assistance dog that are specially trained to do work or perform tasks directly related to a psychiatric disability – thereby allowing them legal public access rights (Americans with Disabilities Act of 1990). For example, PTSD service dogs can be trained to detect a veteran's physical signs of anxiety and distress, serving to alert to and interrupt anxiety and panic attacks during the day as well as interrupt nightmares during the night. PTSD service dogs can also be trained for positional commands thought to provide a sense of safety in public, such as standing behind the veteran in public and "watching their back." The resulting companionship and non-judgmental social support that a PTSD service dog provides can also offer emotional and therapeutic value (Krause-Parello and Morales, 2018). PTSD service dogs are referred to as an complementary intervention as this practice is considered a non-traditional approach to supplement evidence-based care and mainstream therapies (O'Haire and Rodriguez, 2018; Scotland-Coogan et al., 2020). The demand for PTSD service dogs continues to increase, waitlists for PTSD service dogs are often months or years long (Walther et al., 2017, 2019). PTSD service dogs may be popular due to the low perceived stigma surrounding this practice in comparison to other forms of mental health treatment (Kim et al., 2010; Yarborough et al., 2017).

Recent research has provided preliminary evidence of the therapeutic efficacy of PTSD service dogs for military veterans. Cross-sectional studies suggest that compared to receiving usual care while on the waitlist, having a PTSD service dog is associated with lower PTSD symptoms, better quality of life, and better social functioning in addition to more regulated production of the stress hormone cortisol (Yarborough et al., 2017; O'Haire and Rodriguez, 2018; Rodriguez et al., 2018). Similarly, longitudinal studies have found that after receiving a PTSD service dog, veterans self-report significant improvements to PTSD symptoms in addition to secondary outcomes such as depression, anxiety, and quality of life (Kloep, 2016; Bergen-Cico et al., 2018; Whitworth et al., 2019). This emerging literature base is complemented by qualitative reports suggesting that PTSD service dogs can provide significant social and emotional support, reduce stress, and improve veterans' overall quality of life (Taylor et al., 2013; Yount et al., 2013; Krause-Parello and Morales, 2018).

Despite recent knowledge gained regarding the psychosocial and physiological effects of PTSD service dogs, the therapeutic components of the intervention remain largely undefined. Various proposed standards for PTSD service dog training agree that dogs must be trained for tasks to mitigate the veterans' PTSD (Assistance Dogs International, 2019). However, these trained tasks not only vary widely across service dog providers, but also according to an individual veteran's needs (Vincent et al., 2019). There is a critical need for an empirical assessment of the perceived clinically relevant value of specific trained tasks and behaviors for military veterans with PTSD. This information is especially relevant for understanding how these psychiatric service dogs may serve as an complementary treatment option for PTSD. Further, it is unknown how important both untrained and trained behaviors are for managing PTSD symptoms, how often trained tasks are used on a daily basis, and how these outcomes may relate to PTSD symptom severity, time since receiving the service dog, and the human–animal bond. As research in this area reaches the rigor of clinical trials (ClinicalTrials.gov, 2019a,b), such knowledge is crucial to be able to interpret outcomes, understand potential mechanisms of action, and optimize future therapeutic efficacy.

The purpose of this exploratory, non-hypothesis driven study was to define the PTSD service dog intervention by quantifying its therapeutic components utilizing self-reported data from a population of military veterans both with a service dog and on the waitlist to receive one. Specifically, this research aimed to (1) quantify the importance of both trained and untrained service dog behaviors toward veterans' PTSD (2) describe the frequency of use and PTSD symptom specificity of trained service dog tasks, (3) determine how PTSD symptom severity, the veteran-service dog relationship, and time since the service dog was placed may relate to importance and usage outcomes, and (4) compare the expectations of those on the waitlist to the everyday experiences of veterans with service dogs.

# MATERIALS AND METHODS

## Participants

Using a cross-sectional design, participants both with a service dog and on the waitlist to receive a service dog were recruited to participate in an online survey. Participants were recruited between January and May of 2016 from the database of the United States service dog provider K9s For Warriors (Ponte Vedra Beach, FL, United States). K9s For Warriors is an Assistance Dogs International (ADI)-accredited, non-profit organization that provides service dogs free of charge to post-9/11 military veterans in almost all 50 U.S. states. Participants consisted of those who applied for and had been approved to receive a PTSD service dog from K9s For Warriors, which utilizes the following inclusion criteria for placements: Verified honorable discharge or current honorable service in the United States armed forces, verification of a service-connected disability, verified diagnosis of PTSD from a clinician referral letter or met the clinical cutoff of 50 on the PTSD Checklist (PCL-IV; Weathers et al., 1993), passed a background check verifying no conviction of any crime against animals or felony convictions, had no current substance abuse, was independently mobile, and had no more than two pet dogs living in the home (per the policies of the service dog provider).

A total of 217 military veterans with PTSD participated in the survey (response rate of 51%), including 134 placed with a service dog and 83 on the waitlist to receive one. Participants *on the waitlist* had been approved to receive a service dog from the provider (i.e., had completed the application and passed screening from the organization) but had not yet received a service dog at the time of participation in the research. The exact length of time on the waitlist was unknown for each participant, but both previous research with this population (O'Haire and Rodriguez, 2018) and reports from the service dog provider indicate that veterans spend an average of 18 months on the waitlist.

Participants *with a service dog* had received a service dog from the provider between 1 month and 7.17 years prior to participating in the research ($M$ = 1.80, $SD$ = 1.67, Median = 1.33 years). Service dog placement occurred onsite at K9s For Warriors campus during a 3-week class. During this time, groups of 6–10 veterans received daily instruction to learn how to interact with, care for, and continue training their service dogs at home. Service dogs were primarily sourced from shelters and selected based on their age, temperament, and physical size. Specifically, dogs are screened for physical soundness and health, and selected for friendly temperaments, lack of any aggression or fear, and overall trainability. At full maturity, dogs must be at least 24 inches tall and weigh at least 50 pounds to serve as a potential bracing object for veterans needing assistance with balance. Breeds were predominantly Labrador Retrievers or Labrador Mixes. Dogs were trained for a minimum of 120 h before placement on basic obedience (e.g., sit, stay, down, and recall) and specific tasks to mitigate PTSD symptoms (see **Table 1** for the list of tasks trained by the organization). Before final placement, veteran-service dog pairs were required to pass a public access certification test to demonstrate appropriate control and service dog behavior in public settings.

**TABLE 1 |** Service dog trained behaviors and untrained behaviors or characteristics as described to participants in the survey.

| | |
|---|---|
| **Trained behaviors** | |
| Interrupt/alert to anxiety | The dog lets the veteran know when they are feeling anxious and interrupts with a nose bump, placing head in lap, or some other behavior. |
| Calm/comfort anxiety | The dog performs a calming behavior such as making physical contact (laying on top of handler, placing head in lap, gently leaning against the body) when the veteran feels distress or anxiety. |
| Block (create space) | The dog positions itself horizontally in front of the veteran to create personal space. |
| Block (guard/protect) | The dog positions itself horizontally in front of veteran to guard/protect. |
| Cover (watch back) | Dog positions itself directly behind the veteran to "watch" the veteran's back. |
| Social greeting | The dog helps greet people in public by sitting/offering a paw. |
| Wake up from nightmare | The dog recognizes that the veteran is having a nightmare and gently wakes them up. |
| **Untrained behaviors or characteristics** | |
| Companionship | Dog is a "battle buddy," best friend, and companion. |
| Non-judgmental | Dog does not judge person for PTSD. |
| Love | Dog gives person something to love, and to feel loved in return. |
| Calming | The dog's physical presence is calming and comforting. |
| Happiness | Dog makes person smile and brings joy to their life. |
| Independence | Dog is source of empowerment for veteran to do things on their own. |
| Leave house | Dog enables veteran to leave house and feel at ease in public. |
| Connecting to family | Dog helps connect veteran to their family. |
| Routine | Dog adds structure, routine, and responsibility to veteran's life. |
| Social help | Dog helps the veteran make friends and have comfortable social interactions. |

Apart from the service dog intervention, neither the service dog provider nor the researchers encouraged or discouraged any treatments or intervention services for participants' PTSD. Thus, all participants received unrestricted access to usual care for their PTSD symptoms.

## Procedure

The study protocol was approved by the Purdue University Human Research Protection Program Institutional Review Board (IRB Protocol 1607017967). Because there were no interactions between researchers and service dogs, a waiver was obtained by the Purdue University Institutional Animal Care and Use Committee (IACUC). To recruit participants, researchers obtained contact information including veterans' names and email addresses from the service dog provider. Potential participants were recruited via a personalized email which included information about the study and a link to complete an online survey regarding their experiences and perceptions about PTSD service dogs (dog-specific outcomes

including service dog training, temperament, and personality have been published in a separate manuscript; LaFollette et al., 2019). Participants were advised that their individual answers would be kept confidential and would not be shared with the service dog provider. Voluntary informed consent was obtained electronically by asking participants to confirm that they understood the research study and details regarding their participation before clicking "next" on the survey's landing page. Upon completion of the survey, participants chose between receiving $20 in cash (42%) or $20 Amazon gift card (58%) as compensation for their time.

## Measures

### Demographics

The online survey contained demographic questions including age, gender identity, marital status, and current pet dog ownership. Participants also consented for researchers to access their records with the service dog provider, which shared service dog placement information (month and year) for those already placed with a service dog.

### PTSD Symptoms

Posttraumatic stress disorder symptom severity was assessed with the PTSD Checklist (PCL-5) for the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; Blevins et al., 2015). The PCL-5 is a 20-item questionnaire assessing current PTSD symptom severity across four subscales corresponding with the DSM-5 symptom criteria of PTSD: Intrusion, Avoidance, Negative alterations in cognition and mood, and Alterations in arousal and reactivity. The PCL-5 format used omitted the Criterion A component as participants were already screened for having a service-connected PTSD diagnosis. Rather, current symptom severity was assessed by asking participants to rate their symptomology in relation to a general "stressful experience." Participants were asked to rate how often each PTSD symptom has affected them in the past month on a scale of 0 ("Not at all") to 4 ("Extremely"). The scale ranges from 0 to 80, with higher scores indicating greater PTSD symptom severity. Cronbach's α in the current sample was 0.95 overall with subscale α's of 0.91 (B), 0.84 (C), 0.88 (D), and 0.86 (E). A total of 31 participants (14%) did not fill out the PCL-5 measure and thus were excluded from analyses that related PTSD symptom severity to outcomes. A total of 11 participants (5%) had missing values, but completed more than 75% of the PCL-5 ($n = 8$ missing one question, $n = 2$ missing two questions, and $n = 1$ missing three questions), allowing for subscale-level mean imputation of missing values.

### Veteran-Service Dog Closeness

Veterans with a service dog completed the Inclusion of Other in Self (IOS) scale as a measure of their relationship with the service dog. The IOS is a single item, 7-option pictorial scale with demonstrated validity and reliability to measure interpersonal closeness (Aron et al., 1992). The IOS has been previously used as a measure of the human–animal bond (McConnell et al., 2011; LaFollette et al., 2019). The pictorial scale consists of seven diagrams, each with a set of two circles that range from not overlapping (score of 1) to completely overlapping (score of 7). One circle was labeled "you" and the other labeled "service dog." Participants were asked to "Choose the option that best describes the relationship between you and your service dog."

### Importance of Trained and Untrained Service Dog Behaviors

Participants completed a questionnaire quantifying the perceived importance of a list of trained tasks and untrained service dog behaviors (**Table 1**). The questionnaire was developed with advice from service dog providers and experts in the field of human–animal interaction.

Seven trained tasks were assessed in this study based off tasks trained from the service dog provider (**Table 1**). These included the dog's ability to both interrupt and alert to anxiety or distress (including waking from nightmares), as well as positional commands to be used in public such as *block* and *cover*. The *block* command was split into two different variations: block to help provide personal space in public, and block to guard or protect the veteran from others in public. While the physical behavior of the service dog is identical in both versions, the distinction in wording was intentionally chosen to identify differences in veterans' perceived purpose of the behavior.

Ten untrained behaviors and characteristics were assessed based on qualitative reports from veterans with PTSD service dogs (Taylor et al., 2013; Yount et al., 2013; Krause-Parello and Morales, 2018). These included the service dog's companionship, non-judgmental support, source of love, calming presence, source of happiness, source of independence, help leaving the house, help connecting to family members, instilling a routine, and help with social interactions.

For each of the seven trained tasks and ten untrained behaviors, participants were asked on a scale of 1 ("Not at all important") to 5 ("Extremely Important") how helpful the behavior has been for their PTSD (or how helpful the behavior is *expected to be*, for those on the waitlist). A short narrative description accompanied each task or behavior/characteristic to aid in objectivity in interpretation (**Table 1**). An overall importance score was calculated for both trained tasks and untrained behaviors by averaging items. Cronbach's α in the current sample was 0.84 (trained task importance) and 0.87 (untrained behavior importance).

### Frequency of Trained Task Use

For each of the seven trained tasks, participants were asked how often they currently used each task in a typical day (or how often they *expected to use* each task in a typical day, for those on the waitlist). As this was a free response question, most participants provided numerical frequency values, but text entries were possible. Text entries were coded into numeric responses by the research team (e.g., "Never" or "Once a day" were coded to 0 and 1, respectively, while ranges such as "4–5 times" were coded to 4.5). However, for 20 data points from $n = 4$ participants with a service dog and six data points from $n = 2$ participants from the waitlist, text entries were unable to be coded into a specific numeric value and thus were dropped from analysis (e.g., "all the time" or "only when I'm in public").

### PTSD Symptom Specificity of Trained Tasks

Among only participants with a PTSD service dog, participants were given a list of the 20 symptoms from the PCL-5 and asked to indicate the trained tasks that have helped address each symptom using a check all that apply format. Participants were also given the option to indicate "Not Applicable" for any PTSD symptom.

## Analysis Strategy

Analyses were conducted using Statistical Package for the Social Sciences (SPSS 24.0). To compare demographic characteristics by group, independent *t*-tests were conducted for the continuous variable of age and chi-squared tests were conducted for the categorical variables of gender, marital status, and pet dog ownership.

### Importance of Trained and Untrained Service Dog Behaviors

Prior to analyses, importance values were examined for their distribution which determined a high degree of skewness. Importance values were log-transformed, which corrected the skew to a normal distribution. To compare expected and experienced importance of behaviors, a series of linear regressions were conducted which predicted log-transformed importance from the binary variables of having a service dog or not (yes or no) as well as participant gender (male or female), relationship status (single or married/cohabitating), if there was a pet dog in the home (yes or no), and PTSD severity (total PCL-5 score). Age was also considered as an independent variable, but did not have any significant effects in models ($p$'s $> 0.10$). Thus, age was excluded from further models to conserve power. Further, to reduce the number of statistical comparisons made, only the average untrained behavior importance score was compared across groups (rather than item-level comparisons). Within-group *t*-tests compared trained task importance to untrained behavior importance.

Linear regressions were conducted to determine the effect of PTSD severity, veteran-service dog relationship, and time since the service dog was placed on log-transformed perceived importance of behaviors. Independent variables included the demographic covariates above and PTSD severity (total PCL-5 score), as well as veteran-service dog closeness (IOS score) and time since service dog placement (in number of months) for those with a service dog. Cohen's *d* effect sizes were calculated based on the means, standard deviations, and sample sizes of each group using the cutoffs of 0.2 for a small effect, 0.5 for a medium effect, and 0.8 for a large effect (Cohen, 1988).

### Frequency of Trained Task Use

The distribution of frequency values also had a high degree of skewness with several extreme outliers. To account for the fact that these outliers could lead to significant results that might not be representative, data were winsorized such that extreme values were replaced with the trimmed cutoff of three standard deviations from the mean. Using this approach, a total of 24 extreme values from 10 participants were replaced. After winsorizing, residuals did not follow normality assumptions. Winsorized values were then log-transformed, which resulted in normal residuals in subsequent linear regression models.

### PTSD Symptom Specificity of Trained Tasks

For each participant, two scores were calculated. First, the number of tasks that were reported to help each PTSD symptom were summed such that a score of 0 indicated that the participant did not perceive any tasks to help the PTSD symptom (and/or they had indicated "Not Applicable"), and a score of 7 indicated that the participant perceived all seven trained tasks as helping the PTSD symptom. An average of this score was taken across all participants to calculate the average number of trained tasks that helped each PTSD symptom, with a possible score range from 0 to 7. Second, the number of PTSD symptoms that were helped by each trained task were summed such that a score of 0 indicated the participant did not perceive the trained task to help any of the listed PTSD symptoms, and a score of 20 indicated the participant perceived the trained task to help all 20 PTSD symptoms. An average of this score was taken across all participants to calculate the mean number of PTSD symptoms helped by each trained task, with a possible score range from 0 to 20. A total of $n = 10$ participants who completed less than half of the PTSD symptom specificity survey were excluded from these summary scores in order to prevent skewed values.

# RESULTS

## Demographics

Participants with a service dog ($n = 134$) and on the waitlist ($n = 83$) did not significantly differ in age (waitlist $M = 39.63$, $SD = 9.06$ years old; service dog $M = 39.99$, $SD = 8.07$ years old; $t = 0.30$, $p = 0.764$; age missing for $n = 3$ individuals with a service dog and $n = 1$ on the waitlist). In addition, groups did not differ by relationship status (waitlist 67% married or cohabitating, service dog 63%; $X^2 = 0.23$, $p = 0.631$; relationship status missing for $n = 2$ individuals on the waitlist), or whether they had a pet dog in the home or not (waitlist 45%, service dog 50%; $X^2 = 0.60$, $p = 0.437$). However, groups did significantly differ in gender; participants on the waitlist were more likely to be female than those with a service dog (waitlist 66% male, service dog 81% male; $X^2 = 6.59$, $p = 0.010$). Groups significantly differed in PTSD symptom severity, with those on the waitlist reporting more severe PTSD symptoms than those with a service dog (waitlist PCL-5 $M = 58.97$, $SD = 12.96$, service dog $M = 44.34$, $SD = 17.13$; $t = -6.62$, $p < 0.001$; Jensen et al., 2020).

## Importance of Trained Tasks and Frequency of Task Use

**Table 2** displays descriptive statistics of perceived importance and frequency of use of service dog trained tasks. Overall, participants with a service dog reported using a trained task an average of 3.16 ($SD = 2.54$) times a day (**Figure 1**). Veterans with a service dog rated *calm/comfort to anxiety* as both the most important task and the most frequently used task. Similarly, *cover* and *interrupt/alert to anxiety* were rated as the second and third most important and most frequently used tasks, respectively. *Block to create space* and *block to guard/protect* were rated nearly identically for both importance and frequency. Veterans rated the service dog's *social*

*greeting* task as the least important behavior for their PTSD and the second least frequently used task. Perceived importance of the *social greeting* task had the largest variance among veterans with a service dog, indicating the most individual variability in responses. The least frequently used service dog task from veterans was *wake up from nightmare*. It is notable that even the lowest-rated tasks were still perceived on average as "moderately" important for veterans' PTSD. Overall, waitlist expectations of importance and frequency of use of trained tasks tended to be higher than what was experienced among veterans with service dogs (see Results section "Expectations vs. Experiences").

## Importance of Untrained Behaviors

Overall, veterans with a service dog rated the importance of untrained behaviors higher than the importance of trained tasks ($M_{\text{trained}}$ = 3.70 of 5, $M_{\text{untrained}}$ = 4.42; $t$ = −8.50, $p < 0.001$, $d$ = 1.04). **Table 3** contains descriptive statistics regarding veterans' perceived importance of untrained service dog behaviors and characteristics. Veterans with a service dog rated all ten untrained behaviors on average as "quite a bit" to "extremely" important for their PTSD symptoms. The most important untrained behavior for helping PTSD symptoms was the dog's ability to give the veteran something to love and to feel loved in return. The least important untrained behaviors for PTSD were the service dog's ability to connect them to their family and provide social help in public, but most participants on average indicated these behaviors were still "quite a bit" important for their PTSD. However, connecting to family and social help also had large standard deviations indicating that responses for these characteristics were quite varied. Expected importance of untrained behaviors did not significantly differ from what was experienced by those with a service dog (see Results section "Expectations vs. Experiences").

## PTSD Symptom Specificity of Trained Tasks

**Table 4** contains descriptive statistics regarding the perceived helpfulness of each trained task for individual PTSD symptoms as reported by veterans with a service dog. For each trained task, veterans were asked to indicate which PTSD symptoms they were helpful for (if any). Across the seven trained tasks, there was considerable variability in the number of PTSD symptoms helped. However, the most widely relevant service dog task for veterans' PTSD symptoms was *calm/comfort to anxiety*, with veterans reporting this task to help an average of 12.73 of the 20 PTSD symptoms. This task was perceived as applicable to symptoms across all four symptom clusters. The second most widely relevant task was *interrupt/alert anxiety*, helping an average of 6.80 of the 20 PTSD symptoms. Most veterans perceived this task as being helpful to several intrusion symptoms as well as symptoms regarding alterations in arousal and reactivity. The task that veterans reported to help the least amount of PTSD symptoms on average was *social greeting*, helping an average of 1.14 PTSD symptoms. *Wake from nightmares* was also reported to help only 1.76 PTSD symptoms on average a majority of veterans reporting this task to help with intrusive dreams.

On average, the PTSD symptom helped the most by the service dog's trained tasks was hypervigilance, with veterans indicating an average of 2.74 trained tasks (of seven) were helpful toward addressing this symptom. Further, 50% or more of veterans reported that four tasks (*interrupt/alert to anxiety*, *calm/comfort to anxiety*, *block to guard/protect*, and/or *cover/watch back*) helped their hypervigilance. Other PTSD symptoms helped by more than two tasks on average included intrusive memories of the traumatic event ($M$ = 2.38 tasks), feeling jumpy or easily startled (2.28), feeling distressed when reminded of the traumatic event (2.16), and having strong physical reactions (e.g., heart pounding, and sweating) when reminded of the traumatic event (2.12). On the contrary, the PTSD symptoms that were least helped by the service dog's trained tasks included trouble remembering the traumatic event ($M$ = 0.56 of 7 tasks) and engaging in reckless behavior ($M$ = 0.68 tasks). When asked if the service dog's trained tasks helped these two symptoms, 65 and 61% of veterans, respectively, indicated the service dog's training was "not applicable" to these symptoms.

## Effect of PTSD Severity, Veteran-Service Dog Closeness, and Time Since Service Dog Placement

**Table 5** displays analyses examining the relationships between PTSD severity, veteran-service dog closeness, and time since service dog placement with importance and frequency outcomes. Among veterans with a service dog, there was no effect of PTSD symptom severity on trained task importance, untrained behavior importance, or frequency of task use. Specifically, veterans' PTSD symptom severity did not predict how often they used trained tasks in a given day, nor how important they rated trained and untrained behaviors for their PTSD. Among veterans with a service dog, veteran-service dog closeness was a stronger predictor of perceived importance and reported frequency of PTSD service dog behaviors (**Table 5**). Specifically, higher perceived veteran-service dog closeness was associated with higher perceived importance of both trained and untrained behaviors for the veteran's PTSD. Veterans who reported higher closeness with their service dogs also reported using the service dog's trained behaviors more often. There was no significant relationship between time since the service dog was placed and perceived trained task importance or untrained behavior importance. However, time since placement was a significant predictor of frequency of task use such that the longer the veteran had the service dog, the less frequently they reported using trained tasks on a daily basis.

Among veterans on the waitlist, PTSD symptom severity was a significant predictor of expected importance of trained tasks, but not untrained behaviors (**Table 5**). That is, veterans on the waitlist with more severe PTSD expected their future service dogs' trained tasks as being more important for their PTSD than veterans with less severe PTSD symptoms. In addition, PTSD severity was a significant predictor of expected task frequency, such that veterans on the waitlist with more severe PTSD symptoms

**TABLE 2 |** Means, standard deviations and group comparisons of the expected and experienced importance of trained tasks for PTSD symptoms (1 = Not at all important to 5 = Extremely important) and frequency of trained task use per day.

| **Task importance** | **Service dog (*n* = 134)** | | **Waitlist (*n* = 83)** | | **Group difference** | | |
|---|---|---|---|---|---|---|---|
| | ***M*** | ***SD*** | ***M*** | ***SD*** | **β** | ***p*** | ***d*** |
| ***Total*** | 3.70 | 0.82 | 4.21 | 0.68 | −0.22 | 0.005** | 0.68 |
| Calm/comfort anxiety | 4.23 | 0.97 | 4.43 | 0.74 | −0.07 | 0.388 | 0.23 |
| Interrupt/alert to anxiety | 3.98 | 0.97 | 4.36 | 0.79 | −0.06 | 0.447 | 0.43 |
| Cover (watch back) | 3.95 | 1.13 | 4.39 | 0.92 | −0.13 | 0.125 | 0.43 |
| Block (create space) | 3.65 | 1.14 | 4.35 | 0.83 | −0.25 | 0.002** | 0.70 |
| Block (guard/protect) | 3.63 | 1.19 | 4.34 | 0.85 | −0.24 | 0.002** | 0.69 |
| Wake up from nightmare | 3.31 | 1.33 | 4.06 | 1.11 | −0.18 | 0.025* | 0.61 |
| Social greeting | 3.18 | 1.51 | 3.54 | 1.15 | −0.21 | 0.013* | 0.27 |
| **Task frequency** | **Service dog (*n* = 97)** | | **Waitlist (*n* = 63)** | | **Group difference** | | |
| | ***M*** | ***SD*** | ***M*** | ***SD*** | **β** | ***p*** | ***d*** |
| **Total** | 3.16 | 2.54 | 5.23 | 4.08 | −0.21 | 0.019* | 0.61 |
| Calm/comfort anxiety | 5.05 | 4.60 | 6.48 | 4.84 | −0.75 | 0.407 | 0.30 |
| Cover (watch back) | 4.08 | 4.90 | 6.43 | 6.75 | −0.25 | 0.010* | 0.40 |
| Interrupt/alert to anxiety | 3.43 | 2.61 | 5.92 | 4.36 | −0.24 | 0.008** | 0.69 |
| Block (guard/protect) | 2.61 | 4.02 | 5.09 | 5.61 | −0.25 | 0.009** | 0.51 |
| Block (create space) | 2.59 | 4.32 | 5.80 | 6.98 | −0.33 | 0.001** | 0.55 |
| Social greeting | 2.34 | 2.69 | 3.82 | 3.52 | −0.14 | 0.214 | 0.47 |
| Wake up from nightmare | 1.36 | 1.51 | 2.47 | 2.22 | −0.05 | 0.621 | 0.58 |

*Tasks are ordered from highest to lowest mean values within each group. Group difference data includes standardized regression coefficients and p-values controlling for participant gender, relationship status, presence of pet dog in the home, and PTSD severity. Effect sizes are displayed using Cohen's d; *p < 0.05, **p < 0.01.*

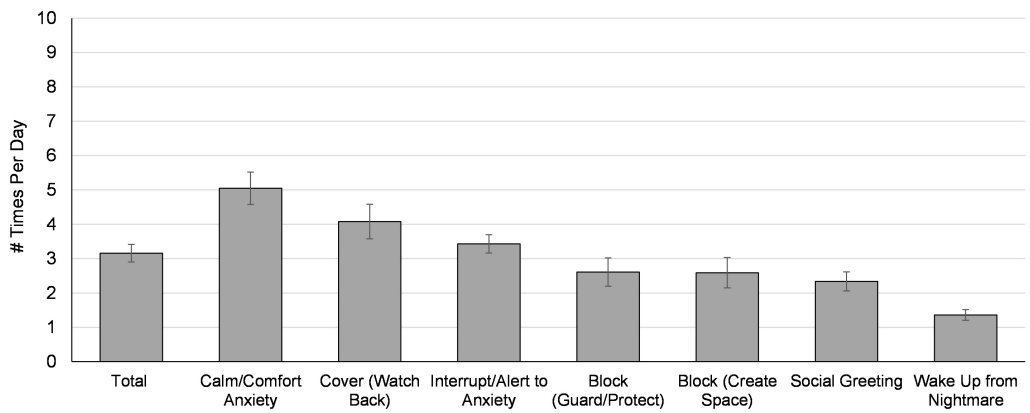


**FIGURE 1 |** Mean frequency of task use in "a typical day" reported by *n* = 97 veterans with a service dog, ordered from highest to lowest values. Error bars represent the standard error of the mean.

expected to use the service dog's trained task more often on a daily basis in the future.

## Expectations vs. Experiences

Overall, waitlist expectations of importance and frequency of use of trained tasks was significantly higher on average than what was experienced among veterans with service dogs. Specifically, after controlling for participant gender, relationship status, presence of a pet dog in the home, and PTSD severity, waitlist participants expected both overall task importance and four of the seven specific trained tasks to be more important for helping their PTSD symptoms than what was experienced by those with a service dog (**Table 2**). Tasks in which expected importance was not higher than experienced were *calm/comfort anxiety*, *interrupt/alert to anxiety*, and *cover*. Regarding frequency of use, participants on the waitlist again expected to use trained service dog tasks more frequently per day than those with a service dog reported. Specifically, veterans on the waitlist expected to use four of seven trained tasks (*cover*, *interrupt/alert to anxiety*, *block to guard/protect*, *and*

**TABLE 3 |** Means and standard deviations of the expected and experienced importance for PTSD symptoms (1 = Not at all important to 5 = Extremely important) of untrained service dog behaviors, ordered from highest to lowest values within each group.

| Untrained behavior/characteristics importance | Service dog ($n$ = 134) | | Waitlist ($n$ = 83) | | Group difference | | |
|---|---|---|---|---|---|---|---|
| | *M* | *SD* | *M* | *SD* | β | *p* | *d* |
| **Total** | 4.42 | 0.54 | 4.41 | 0.56 | 0.05 | 0.534 | 0.02 |
| Love | 4.79 | 0.52 | 4.70 | 0.66 | | | |
| Companionship | 4.75 | 0.53 | 4.67 | 0.57 | | | |
| Calming | 4.67 | 0.67 | 4.66 | 0.65 | | | |
| Happiness | 4.64 | 0.60 | 4.55 | 0.79 | | | |
| Non-judgmental | 4.51 | 1.13 | 4.61 | 0.87 | | | |
| Routine | 4.42 | 0.75 | 4.20 | 0.93 | | | |
| Independence | 4.29 | 0.85 | 4.42 | 0.80 | | | |
| Leave house | 4.29 | 0.88 | 4.40 | 0.90 | | | |
| Social help | 3.95 | 1.06 | 3.96 | 1.10 | | | |
| Connecting to family | 3.92 | 1.17 | 3.90 | 1.11 | | | |

*Group difference analysis includes the standardized regression coefficient and p-value controlling for participant gender, relationship status, presence of pet dog in the home, and PTSD severity.*

*block to create space*) more frequently than what was reported by those with a service dog (**Table 2**). Similar to veterans with a service dog, those on the waitlist expected to use *calm/comfort to anxiety* the most often per day, followed by *cover* (*watch back*).

Expected importance of untrained behaviors did not significantly differ from what was experienced by those with a service dog (**Table 3**). However, both groups reported near-ceiling importance for all 10 untrained behaviors and characteristics. Aligning with experiences from those with a service dog, veterans on the waitlist perceived the service dog's ability to give the veteran something to love and to feel loved in return as the most important untrained service dog characteristic. Similarly, veterans on the waitlist reported the service dog's ability to connect them to their family and provide social help in public as the least important untrained behaviors for PTSD. Overall, veterans on the waitlist rated the expected importance of untrained behaviors significantly higher than trained tasks ($M_{\text{untrained}}$ = 4.41, $M_{\text{trained}}$ = 4.21; $t$ = 2.07, $p$ = 0.040, $d$ = 0.32).

Among the waitlist, PTSD symptom severity was a significant predictor of expected trained task importance and frequency of task use, but this relationship was not found for veterans with a service dog (**Table 5**). However, among both groups there was no relationship between PTSD severity and perceptions of the importance of untrained behaviors.

# DISCUSSION

## General

The overall aim of this research was to both document and quantify the therapeutic use of PTSD service dogs to define the intervention while comparing relative expectations of those on the waitlist to everyday experiences of those with a service dog. The specific objectives of this research were to (1) quantify the importance of trained and untrained service dog behaviors toward alleviating PTSD symptoms, (2) quantify how often trained tasks are used while describing their PTSD symptom specificity (2) determine how PTSD symptom severity, the veteran-service dog relationship, and time since the service dog was placed may relate to importance and frequency outcomes, and (3) compare the expectations of those on the waitlist to the everyday experiences of veterans with service dogs. Results from this study offer valuable knowledge toward understanding the specific components and therapeutic value of PTSD service dogs, the PTSD symptoms that are helped most by the service dog's trained tasks, and quantifying the PTSD service dog intervention among a large and representative sample of military veterans both with a service dog and on the waitlist to receive one.

## Trained Tasks

The first objective served to quantify critical components of the PTSD service dog intervention by describing the perceived importance and frequency of use of the service dog's trained tasks. Although there was a moderate degree of individual variance observed, results suggest that all seven trained tasks were, in some capacity, valuable aspects of the PTSD service dog intervention from the perspective of this population. Among those with a service dog, all seven tasks were rated on average as "moderately" to "quite a bit" important for veterans' PTSD. Trained service dog tasks were used on average 3.16 times per day, with individual tasks ranging from an average of 1.36–5.05 times per day. While some trained tasks were broader in their helpfulness toward PTSD symptoms than others, veterans with service dogs reported that all seven trained tasks helped at least one PTSD symptom on average. Results provide critically necessary quantification of the perceived importance, use, and PTSD symptom specificity of psychiatric service dogs' trained tasks.

The trained tasks of *calm/comfort to anxiety* and *interrupt/alert to anxiety* were among the most centrally valued trained tasks for veterans' PTSD. These tasks were not only the most important for veterans' PTSD symptoms, but were also among the most frequently used tasks and rated to help

**TABLE 4 |** Means, standard deviations, and population percentages of the PTSD symptom specificity of trained behaviors.

| DSM-V symptom cluster | PTSD symptom (PCL-5) | *M* (*SD*) tasks helped | Calm/comfort anxiety | Interrupt/alert to anxiety | Block (guard/protect) | Block (create space) | Cover (watch back) | Wake up from nightmare | Social greeting | Not applicable |
|---|---|---|---|---|---|---|---|---|---|---|
| Intrusion | Memories | 2.38 (1.53) | 84% | 60% | 16% | 13% | 27% | 34% | 12% | 5% |
| | Dreams | 1.68 (1.19) | 57% | 40% | 5% | 2% | 5% | 56% | 1% | 18% |
| | Flashbacks | 2.00 (1.40) | 75% | 60% | 16% | 16% | 15% | 12% | 4% | 12% |
| | Cued distress | 2.16 (1.46) | 86% | 56% | 22% | 22% | 16% | 8% | 5% | 5% |
| | Cued physical reactions | 2.12 (1.35) | 85% | 54% | 21% | 22% | 15% | 11% | 3% | 5% |
| Avoidance | Avoiding internal reminders | 1.71 (1.51) | 70% | 41% | 17% | 14% | 15% | 9% | 6% | 22% |
| | Avoiding external reminders | 1.86 (1.84) | 59% | 32% | 29% | 35% | 21% | 4% | 8% | 24% |
| Negative alterations in cognition and mood | Amnesia | 0.56 (1.05) | 27% | 10% | 6% | 5% | 5% | 3% | 1% | 65% |
| | Negative beliefs | 1.42 (1.46) | 68% | 20% | 16% | 8% | 15% | 5% | 11% | 23% |
| | Blame | 1.07 (1.18) | 56% | 21% | 7% | 7% | 7% | 4% | 4% | 32% |
| | Negative feelings | 1.48 (1.30) | 74% | 34% | 13% | 7% | 13% | 2% | 3% | 19% |
| | Loss of interest | 1.36 (1.64) | 51% | 22% | 18% | 14% | 14% | 1% | 15% | 22% |
| | Detachment | 1.50 (1.59) | 65% | 18% | 17% | 16% | 13% | 0% | 22% | 17% |
| | Numbing | 1.15 (1.11) | 68% | 21% | 6% | 8% | 2% | 1% | 9% | 19% |
| Alterations to arousal and reactivity | Irritability/aggression | 1.92 (1.37) | 74% | 62% | 16% | 25% | 10% | 1% | 4% | 9% |
| | Reckless behavior | 0.68 (1.13) | 24% | 21% | 8% | 7% | 5% | 1% | 1% | 61% |
| | Hypervigilance | 2.74 (1.76) | 76% | 50% | 54% | 37% | 50% | 1% | 7% | 10% |
| | Startle | 2.28 (1.70) | 76% | 35% | 38% | 33% | 43% | 1% | 3% | 13% |
| | Concentration | 1.48 (0.97) | 52% | 25% | 7% | 13% | 8% | 0% | 2% | 33% |
| | Sleep | 1.30 (1.17) | 63% | 14% | 13% | 3% | 9% | 28% | 0% | 20% |
| | M (SD) symptoms helped | | 12.73 (4.98) | 6.80 (4.68) | 3.37 (3.68) | 3.05 (3.56) | 3.03 (3.24) | 1.76 (2.14) | 1.14 (1.90) | 4.22 (4.11) |

*Percentages represent the proportion of n = 120 veterans with a service dog who indicated that a given task helped each PTSD symptom, with darker colors indicating higher proportions and lighter colors indicating lower proportions. Average tasks helped represents the mean number of tasks (of 7) indicated to help each PTSD symptom by the overall sample. Average symptoms helped represents the mean number of PTSD symptoms (of 20) helped by each trained task for the overall sample. PTSD symptoms are ordered based on the PTSD checklist for DSM-5 (PCL-5), while trained tasks are ordered right to left based on the highest to lowest number of average PTSD symptoms helped.*

**TABLE 5 |** Relationship of PTSD severity, veteran-service dog closeness, and time since placement with importance of untrained behaviors and trained tasks for PTSD symptoms and frequency of task use among veterans with service dogs or on the waitlist.

| | Service dog (*n* = 111) | | | | | | Waitlist (*n* = 71) | |
|---|---|---|---|---|---|---|---|---|
| | PTSD severity | | Veteran-service dog closeness | | Time since placement | | PTSD severity | |
| | β | *p* | β | *p* | β | *p* | β | *p* |
| Untrained behavior importance | −0.13 | 0.157 | 0.40 | <0.001*** | −0.03 | 0.776 | 0.09 | 0.437 |
| Trained task importance | −0.04 | 0.666 | 0.35 | <0.001*** | 0.03 | 0.790 | 0.49 | <0.001*** |
| Task frequency | 0.15 | 0.137 | 0.41 | <0.001*** | −0.36 | 0.001** | 0.41 | 0.001** |

*Data displayed includes standardized regression coefficients and p-values controlling for participant gender, relationship status, and presence of pet dog in home; **p < 0.01, ***p < 0.001.*

the most number of individual PTSD symptoms. For example, *calm/comfort to anxiety* was reported as the most important task for PTSD (4.23 out of 5), the most frequently used task (5.05 times per day), and the task that helped the most number of specific PTSD symptoms (12.73 out of 20 symptoms on the PTSD Checklist). Similarly, *interrupt/alert to anxiety* was perceived as the second most important task (3.98 out of 5), the third most frequently used task (3.43 times a day) and helped the second most number of specific PTSD symptoms (6.80 out of 20 symptoms). These findings mirror qualitative reports suggesting that these anxiety-reducing service dog behaviors are valued by veterans for reducing hypervigilance and coping with re-experiencing episodes (Vincent et al., 2017a; Yarborough et al., 2017; Bergen-Cico et al., 2018; Crowe et al., 2018; Krause-Parello and Morales, 2018). For example, in a 2017 qualitative study of the benefits of psychiatric service dogs, veterans described how the "nudging" behavior from their service dogs during a flashback episode served to help their PTSD by interrupting the distress, "grounding" the veteran, and reminding the veteran to stay in the present (Yarborough et al., 2018). Previous research with non-PTSD populations has also found that simply having a dog present when experiencing distress reduces both subjective stress (Lass-Hennemann et al., 2014) and objective, physiological biomarkers of stress (Polheber and Matchock, 2013). Overall, findings from this research indicate that the service dog's ability to respond to the veteran's distress and serve as a calming presence during anxiety episodes are key mechanistic components of the PTSD service dog intervention.

The *cover* task was the second most frequently used task (4.1 times a day) and was reported to help the PTSD symptoms of hypervigilance and feeling "jumpy" or easily startled. This "watch my back" task is thought to replicate aspects of military comradery in which soldiers will guard each other's blind spots during combat. Previous qualitative reports have described the value of the *cover* task for reducing hypervigilance in public; veterans describe how their service dogs help "share the burden" of being continuously on alert or aware of approaching people (Yarborough et al., 2018). Interestingly, use of this task had the most variability among participants. Because *cover* is largely encouraged to be used when the veteran is hypervigilant of approaching people (such as in public), the observed variation in the frequency of use may be due to the range of experiences and needs from this population. For example, veterans who frequently engage in public activities may also use the cover task more frequently than a veteran who leaves their house less often. Future research may benefit from examining how veterans use tasks differently in different settings during the trajectory of their recovery and reintegration into society over time.

The *social greeting* task helped an average of 1.14 of 20 PTSD symptoms, thus was less broadly applicable to PTSD symptoms than other trained tasks. However, the task was still rated as "moderately" important on average for participants' PTSD. Similar to *cover*, the *social greeting* task is trained to especially assist veterans while in public when interacting with other people. Thus, veterans that go out in public more may both use this task more frequently and perceive greater benefit from the task toward alleviating PTSD symptoms such as detachment from others. Research has shown that both pet dogs and service dogs can be useful as a "social bridge" to facilitate social interaction with strangers (e.g., Eddy et al., 1988; McNicholas and Collis, 2000). Additionally, research has found that veterans with PTSD service dogs report less social isolation and more social participation than veterans on the waitlist for a service dog receiving treatment as usual (Bergen-Cico et al., 2018; O'Haire and Rodriguez, 2018; Whitworth et al., 2019). In this context, the *social greeting* task may serve as a key component of this observed improvement in social interactions.

The *wake up from nightmare* task, in which the dog recognizes signs of physical distress in the veteran at night and wakes them from sleep, was also more specific in the PTSD symptoms that were helped. Although this task did not have the breadth of addressing many PTSD symptoms, it had more specificity in targeting PTSD symptoms such as intrusive memories, nightmares, and sleep disturbances. This finding aligns with qualitative reports describing how veterans have benefited from their service dog's ability to interrupt nightmares and improve sleep quality (Krause-Parello and Morales, 2018; Yarborough et al., 2018). In the current study, 57% of veterans reported that this task helped them with their trauma-related nightmares. It is unknown whether the remaining veterans may have had minimal nightmare symptomology or may have had service dogs that did not actively engage in nightmare-awakening behavior. Regardless, for those veterans that benefit from this trained task, the service dog's interrupting behavior during nightmares appears to be an important aspect of the PTSD service dog intervention.

Interestingly, neither veterans with a service dog nor on the waitlist rated the two different versions of *block* – *block to create personal space* and *block to guard/protect* – differently in terms of importance, frequency, or value for PTSD symptoms. The *block* task has specifically been subject to controversy; mental health professionals have argued that using block may encourage the veteran to maintain fear and avoidance behaviors in public, which is contradictory to the goals of traditional exposure treatment for PTSD (Kloep et al., 2017). While our research did not specifically quantify this potential relationship, results do suggest that military veterans perceived both versions of *block* to be "moderately" to "quite a bit" important for their PTSD, on average. A second criticism of the *block* task is that its perceived use to guard or protect the veteran from others may perpetuate and reinforce negative views about their environment. While slightly more veterans with a service dog reported *block to guard or protect* as addressing their hypervigilance than *block to create personal space*, frequency of use of either version of the task was not significantly related to the veteran's current PTSD symptomology. The two versions of *block* may not have been rated differently due to participants not perceiving the nuances of the differential survey wording. For example, some veterans may have perceived *block to guard and protect* as inherently allowing for personal space. In a 2018 qualitative study, veterans described how their service dogs' stature and presence created a physical barrier between them and others in public to both prevent individuals from coming too close *and* creating a sense of security (Lessard et al., 2018). Future research will be necessary to elucidate the underlying perceptions of veterans who regularly use the *block* task and how it relates to their avoidance symptomology and views regarding their social environment.

## PTSD Symptom Specificity

Among veterans with a service dog, trained tasks addressed almost every PTSD symptom from the DSM-5. On average, intrusion symptoms were helped by the most number of tasks. That is, veterans reported that their service dogs helped mitigate intrusive memories or flashbacks of the traumatic experience as well as internal and physical distress from the memories. These symptoms were mainly addressed by the trained tasks of *calm/comfort to anxiety* and *interrupt/alert to anxiety*. In this context, the service dog's calming presence and interrupting behaviors (e.g., licking and pawing) can serve to anchor the veteran in the present, thereby distracting them from the flashback while providing a calming sense of relief from the internal and/or external distress.

The two PTSD symptoms that were not helped for a majority of veterans with service dogs were amnesia (i.e., having trouble remembering parts of the traumatic experience) and engaging in risky or reckless behavior. This finding is to be expected since research has suggested that service dogs are not a standalone "cure" for PTSD. Rather, PTSD service dogs are an complementary treatment to address symptoms as a supplement to evidence-based treatment (O'Haire and Rodriguez, 2018). Thus, it is unrealistic to expect a service dog to address all aspects of PTSD symptomology. In a 2017 longitudinal study, veterans' PTSD symptomology significantly decreased with clinically meaningful change after 3 months with a PTSD service dog, but only 12 of the 17 PCL symptoms showed significant improvement on an item-level (Vincent et al., 2017b). Both this research as well as current findings provide specificity regarding the PTSD symptoms that are both helped and not helped by service dogs. This information is not only critical to guide clinician's understanding of how these service dogs may benefit PTSD symptomology, but is also important knowledge for service dog providers when educating potential and current clients on how a service dog may help PTSD.

## Untrained Behaviors

Overall, the service dogs' untrained behaviors were considered more important than trained tasks for veterans' PTSD. Specifically, among both those with and without a service dog, 8 of the 10 behaviors or characteristics were rated "quite a bit" important for their PTSD (on a scale from "not at all" to "extremely"). These included aspects of the service dog that can also be shared by a pet dog or an emotional support dog such as the dog's ability to provide companionship, non-judgmental support, love, a calming presence, happiness, and a sense of routine. In a 2013 survey of 30 military veterans with PTSD who benefited from their pet dogs, veterans similarly reported feeling calmer, less lonely, and less depressed from their dog's companionship (Stern et al., 2013). However, although most veterans reported that their pet dogs tried to "cheer me up when I'm feeling bad," there was no significant impact of the pet dog on the PTSD symptoms of intrusive memories, flashbacks, or nightmares (Stern et al., 2013). Overall, results from both the Stern et al. (2013) study and the current research suggest that untrained aspects of canine companionship, inherent to most pet dogs, may be therapeutic for the mental and social health of military veterans with PTSD. However, in addition to the helpfulness of the service dog's specific training toward interrupting and calming anxiety and assisting the veteran in public, this research found that characteristics specific to service dogs (e.g., providing a sense of independence, allowing the veteran to leave the house, and feeling at ease in public) were rated just as highly as the other untrained behaviors such as providing love and companionship. Future research is necessary to fully disentangle how the service's untrained and trained behaviors may dually contribute to the therapeutic components of the PTSD service dog intervention. Considering the costs and long waitlists associated with preparing and placing trained service dogs, further research is warranted to determine the potential value of pet dogs and emotional support dogs for this population as an alternative.

## Effects of PTSD Severity, Veteran-Service Dog Closeness, and Time Since Placement

Surprisingly, results showed that PTSD severity was not an important significant predictor of task importance or frequency of use among those with a service dog. Specifically, the severity

of a veteran's PTSD did not have a significant relationship with how important the veteran perceived his or her service dog's trained or untrained behaviors, nor how often he or she used most trained tasks on a daily basis. These null findings may be partially due to the wide variety of experiences from those with a service dog. For example, one might assume that veterans with more severe PTSD both use trained tasks more frequently and view those tasks as more important. However, some veterans with severe PTSD may infrequently leave their house or engage with strangers resulting in less use of tasks that are most suited to being in public, such as the *cover* or *block* tasks. On the other hand, one might assume that veterans with sub-clinical PTSD may use their service dog's trained tasks less often due to decreased need. However, veterans who are actively reintegrating into society may be using their service dog's tasks more often to help mitigate symptoms (e.g., in a school or workplace environment). Thus, these individual variances may have diluted any clear relationship on a population level.

Veteran-service dog closeness was a significant predictor of both perceived importance and frequency of use of trained tasks. The closer a veteran perceived their service dog to themselves on the IOS scale, the more they viewed their service dog's tasks as important for their PTSD and the more frequently they used the tasks. Veteran-service dog closeness was also positively related to the importance of untrained service dog behaviors. These findings confirm the important moderating relationship that the veteran-service dog bond has in explaining PTSD service dog use and benefits. However, the causational direction of this finding is unable to be determined. Specifically, it remains unclear whether obtaining the benefits of a service dog's trained or untrained behaviors leads to higher perceived closeness, or if veterans with a closer relationship with their dogs perceive their service dog to be more therapeutic for their PTSD. However, it is likely that some of the service dog's trained tasks such as waking from nightmares or alerting to rising anxiety or distress require a certain degree of closeness between the veteran and service dog to precede frequency. Indeed, qualitative reports have suggested that as the bond grows stronger between the veteran and service dog, the dog becomes more likely to become sensitive to the veteran's 'triggers' and emotional state in order to alert to the veteran's anxiety, intervene during a flashback, and/or wake him or her from nightmares.

Finally, time since placement of the service dog was a significant predictor of frequency of trained task use. Specifically, veterans who have had their service dogs for longer reported using trained service dog tasks less often than veterans who have had their service dogs for shorter periods. This finding partially supports a popular stance of the PTSD service dog community that reliance on a PTSD service dog decreases over time as the veteran builds healthy coping skills, reintegrates into society, and decreases avoidance behaviors in public. However, our analyses did not take into consideration engagement with other PTSD treatments over time, which may be an important moderating factor of task use. Future, longitudinal research is necessary to fully understand how the use of trained tasks may vary over time and across individual.

## Expectations vs. Experiences

Overall, results suggest that veterans on the waitlist reported higher expectations than what was experienced by those already with a service dog. Specifically, veterans on the waitlist to receive a service dog expected the service dog's trained tasks to be more important for their PTSD and used more frequently on a daily basis than what was reported by veterans with a service dog. Veterans on the waitlist with more severe PTSD symptoms also expected service dogs' trained tasks to be more important for their PTSD and to use these tasks more often compared to veterans on the waitlist with less severe PTSD. These findings may be explained partly by veterans' feelings of hope and excitement regarding their future PTSD service dog, which may not necessarily be a bad thing. In cognitive-behavioral interventions for PTSD and other types of anxiety disorders, this positive motivational state of hope and optimism may actually play a role in treatment success by mediating clinical improvement (Snyder et al., 2000; Gilman et al., 2012).

On the other hand, there is value in education regarding what to expect from a PTSD service dog. While this research did not directly assess veterans' expectations regarding potentially negative aspects of the service dog intervention, qualitative research with this population has indicated discrepancies between expectations and actual experiences in terms of drawbacks of having a service dog are important. For example, veterans who recently received a service dog report difficulty in coping with the added stressors of maintaining the dog's training, integrating the dog into their family, and receiving unwanted attention in public (Yarborough et al., 2018). In addition, one crucial expectation is that sometimes improvements in PTSD symptoms and quality of life may not be immediate, and the initial transition period of integrating the PTSD service dog into the veteran's life may create additional stress, anxiety, and fatigue (Yarborough et al., 2018). In a 2019 survey of PTSD service dog providers, difficulties including discrepancies in the veteran's and program's expectations as well as problems with maintaining at-home training were both reported to lead to dropouts (Vincent et al., 2019). In fact, research supports that conducting interventions with patients regarding what to expect from a given treatment can have meaningful effects on improving dropout, satisfaction, and even treatment success (Noble et al., 2001). Regardless of the specific goals and motives that a veteran has for applying for a PTSD service dog, it is important for service dog providers, mental health professionals, and occupational therapists involved in treatment decisions to instill accurate expectations regarding the therapeutic value and potential drawbacks of a PTSD service dog.

## Limitations

This research is not without its limitations. First, the study population was recruited from a single, national service dog provider. We do not know if our findings would be replicated if we had surveyed populations that had received dogs from other PTSD service dog providers. Not only do different providers have varying training philosophies and models (e.g., programs in which the veteran is entirely hands-on in training their service

dog), but not all providers train for the same service dog tasks (Vincent et al., 2019). Therefore, future research and replication are necessary to disentangle provider-specific variation in PTSD service dog task use and efficacy. Additionally, the population was limited to military veterans who had experienced service-related trauma. Thus, findings may not generalize to other populations of trauma survivors. Second, a participation bias may have been present such that veterans with a service dog who chose to participate in this research may have had comparatively more positive experiences with their service dogs than those who declined to participate. Veterans who had experienced negative outcomes from obtaining a service dog were also likely not in our participant pool as these individuals often return their service dogs to the provider. As the psychiatric service dog field grows, researchers should begin to quantify both when and why a PTSD service dog may not be efficacious for PTSD symptoms for some individuals. Finally, this research did not aim to quantify past history of stressful life events and specific sources of trauma, but rather assessed currently symptomology via the PCL-5 in relation to a general stressful event. This may have resulted in a mismatch in symptom identification to other current or past sources of trauma. This study also did not quantify other treatments and interventions that veteran participants were engaging in for their PTSD apart from a service dog. However, both trauma type/history and engagement with other PTSD treatments (e.g., medications and psychotherapy) may have important influence on experiences and perceived value of PTSD service dogs. Future research will benefit from examining how these individual differences may explain potential variance in how veterans are incorporating their PTSD service dogs into their lives.

One population limitation is that groups were not equal on all demographic variables; more females were on the waitlist to receive a service dog than already placed with a service dog. The service dog provider schedules separate placement classes for males and females. Thus, this observed difference is likely due to sampling at a time before a large female-only class had occurred. We attempted to control for this limitation by controlling for gender in all models. Participants' race and ethnicity were also not collected, nor was time spent on the waitlist, which may have explained outcome variance. Another limitation of this research is that it relies on self-reported accounts, so recall or expectancy biases may have been present. However, most of the constructs in this study were subjective experiences in nature, such as the perceived importance of the service dog's behaviors and perceived closeness with the service dog. Thus, self-reported data was critical to the research question. A final limitation is that we did not exclude veterans who had recently received their service dogs from participation. This decision was made to both maximize sample size and variability in exploring the effects of time since service dog placement on outcomes. Many service dog providers suggest that most veterans require an initial adjustment period of up to 6 months to develop a bond with the service dog and integrate the dog into their routines and lives. Therefore, some variation observed in importance, frequency, and value of trained tasks may have been partially due to the inclusion of veterans who may have still been in this adjustment period. Future longitudinal research will be necessary to determine how the use and perceived value of PTSD service dogs may evolve over the initial time following placement.

## Conclusion

In conclusion, these results provide valuable quantification of the critical components of the PTSD service dog intervention while describing the everyday experiences and expectations surrounding PTSD service dog's behaviors. This information is critical for advancing our understanding of how and why PTSD service dogs are beneficial for improving PTSD symptomology and quality of life.

The first two objectives of this research documented how important certain service dog behaviors are for a veteran's PTSD symptoms while quantifying how often trained service dog tasks are used on a daily basis. Findings determined that military veterans with a service dog viewed the dog's calming and interrupting behaviors when experiencing anxiety as the most important trained tasks for their PTSD, among the most frequently used tasks in a typical day, and the tasks that helped the most number of PTSD symptoms. However, all seven trained service dog tasks were rated as at least "moderately" important for PTSD, used on average at least once per day, and helped almost all of 20 PTSD symptoms except amnesia and reckless behavior. Further, results suggest that the untrained qualities of a PTSD service dog are essential to their therapeutic value; veterans viewed most untrained behaviors and characteristics as "extremely" important for their PTSD, including the dog's source of love and companionship. Findings provide a much-needed quantification of the clinically relevant value of PTSD service dogs beyond purely qualitative, free-response research.

The second objective of this research aimed to understand how individual differences may contribute to outcomes and change over time. Findings suggest that veteran's PTSD symptoms did not predict either their perceptions of the importance of their service dog's behaviors or the use of the service dog's trained tasks in a typical day. However, veterans who reported feeling closer to their service dogs tended to report using trained tasks more often, and veterans who had their service dogs for longer reported using trained tasks less often. Those reporting more veteran-service dog closeness also viewed the service dog's trained tasks as more important for their PTSD. Not only are these findings critical within the context of interpreting outcomes in future longitudinal, controlled trials, but they also shed light on the substantial contribution of the human–animal bond in the PTSD service dog intervention.

As a final objective, this research compared expectations of veterans on the waitlist to receive a service dog to the everyday experiences of veterans with a service dog. Findings suggest that, on average, individuals on the waitlist not only expected to use their service dogs more often than what was experienced, but also expected trained tasks to be more important for their PTSD symptoms. Veterans' PTSD severity also had a significant positive relationship with how important they expected the service dog's trained tasks to be for their symptoms, in addition to how frequently they expected to use these tasks daily. These findings specifically help to enable providers, practitioners, and veterans to

recognize what to expect from service dogs as a complementary treatment for PTSD.

Overall, this study's findings contribute to emerging knowledge on psychiatric service dogs as a potential complementary treatment option for military veterans with PTSD. This study documented how often trained service dog tasks are used, how important each task is for managing PTSD symptoms, and how these outcomes may relate to PTSD symptom severity, the human–animal bond, and time since receiving the service dog. This research provides critical information to not only interpret research outcomes, but also to optimize future therapeutic efficacy of the PTSD service dog intervention.

## DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Purdue University Institutional Review Board. The patients/participants provided their voluntary informed consent to participate in this study. The animal study was reviewed and approved by Purdue University Animal Care and Use Committee.

## AUTHOR CONTRIBUTIONS

KR, ML, NO, and MO'H contributed to the design of the research and development of the online survey. ML and KR contributed to data curation. KR, KH, and MO'H performed the statistical analyses, with KR and KH writing the results section of the manuscript. KR wrote the first draft of the Introduction, Materials and Methods, and Discussion sections of the manuscript. All authors contributed to manuscript revision and editing and approved the final submitted manuscript.

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REVIEW
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# The Innate Immune System and Inflammatory Priming: Potential Mechanistic Factors in Mood Disorders and Gulf War Illness

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Gulf War Illness is a chronic multisystem disorder affecting approximately a third of the Veterans of the Gulf War, manifesting with physical and mental health symptoms such as cognitive impairment, neurological abnormalities, and dysregulation of mood. Among the leading theories into the etiology of this multisystem disorder is environmental exposure to the various neurotoxins encountered in the Gulf Theatre, including organophosphates, nerve agents, pyridostigmine bromide, smoke from oil well fires, and depleted uranium. The relationship of toxin exposure and the pathogenesis of Gulf War Illness converges on the innate immune system: a nonspecific form of immunity ubiquitous in nature that acts to respond to both exogenous and endogenous insults. Activation of the innate immune system results in inflammation mediated by the release of cytokines. Cytokine mediated neuroinflammation has been demonstrated in a number of psychiatric conditions and may help explain the larger than expected population of Gulf War Veterans afflicted with a mood disorder. Several of the environmental toxins encountered by soldiers during the first Gulf War have been shown to cause upregulation of inflammatory mediators after chronic exposure, even at low levels. This act of inflammatory priming, by which repeated exposure to chronic subthreshold insults elicits robust responses, even after an extended period of latency, is integral in the connection of Gulf War Illness and comorbid mood disorders. Further developing the understanding of the relationship between environmental toxin exposure, innate immune activation, and pathogenesis of disease in the Gulf War Veterans population, may yield novel therapeutic targets, and a greater understanding of disease pathology and subsequently prevention.

**Keywords: Gulf War Illness, mood disorders, neuroinflammation, microglia, therapeutics, innate immunity, cytokines, inflammation**

## INTRODUCTION

Gulf War Illness (GWI) is a chronic multi-symptom illness affecting approximately one-third of the 700,000 U.S. troops deployed to the Persian Gulf region to combat the invasion of Kuwait in 1990–1991 (1). During the intervening conflict, deployed troops were exposed to a myriad of neurotoxins previously unseen during wartime. Soldiers were exposed to two classes of acetylcholinesterase inhibitors: organophosphates in the form of pesticides, and chemical weapons, as well as carbamates in the form of pesticides and the prophylactic anti-nerve agent treatment pyridostigmine bromide. Additionally, deployed troops were exposed to other insecticides and insect repellants such as permethrin, N, N-Diethyl-meta-toluamide (DEET), and lindane. Additional exposures to hazards include smoke from oil well fires and depleted uranium used in armor piercing rounds (2) (**Figure 1**).

Upon returning home, deployed Gulf War Veterans (GWV) started exhibiting constellations of symptoms including fatigue, gastrointestinal disturbances, dermatologic pathology (especially rashes), and cognitive impairment, which could not be reliably explained by the presence of other illnesses. As a result, large scale longitudinal studies were undertaken to investigate the relationship between those who served in the Persian Gulf and the development of these symptoms. These symptoms exhibit a high prevalence throughout all demographics of society, however when compared to non-deployed veterans a significant unexplained increase in the rates of these symptoms is noted in those deployed to the Gulf (3).

The prevalence of chronic multi symptom illness (CMI) is nearly double in deployed vs non-deployed GWV (28.9% vs 15.8%) (4). However, the occurrence of CMI in non-deployed veterans does raise interesting questions. CMI has now also been reported in veterans of the more recent wars in Iraq and Afghanistan, although to a lesser degree than in GWV. Rates of CMI are higher in deployed vs non-deployed veterans of the Iraq and Afghanistan wars (5). A potential explanation for this phenomenon is that physical and psychological stressors experienced during military training may stimulate CMI in certain predisposed individuals. Veterans of the Iraq and Afghanistan wars were also exposed to toxic smoke from burn pits on military bases (6). Thus, it is possible that stress from training or combat may act as a priming factor which later synergizes with inflammatory toxins (i.e. pesticides and nerve agents in Gulf War Veterans or toxic smoke from burn pits in later generation Veterans) to produce CMI.

Disruption of the innate immune system and inflammation has been correlated with GWI (7). Veterans presenting with the disease show alterations in brain structures and in the integrity of the blood-brain barrier mediated by the immune system. Indeed, brain function in GWI is identical to that found in other immune-related conditions (8) and consequently, GWI has been proposed to be studied as a neuroimmune disease (9). GWI animal models have validated the involvement of neuroinflammatory mechanisms in the pathology of the disease (10), including the over-reactivity of astrocytes and microglia. This increased activation of immune cells was also directly observed in the brain of veterans with GWI (11), while

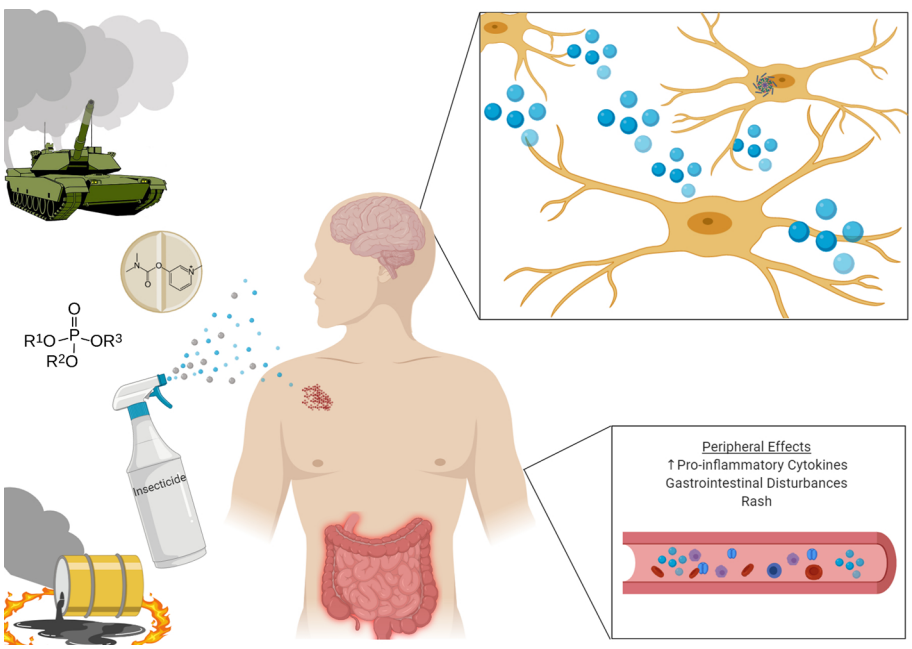


**FIGURE 1 |** Veterans deployed to the Gulf Theatre were exposed to a wide array of neurotoxins, with potent neuroinflammatory effects. Upon return from deployment, many Veterans developed constellations of symptoms including rash, gastrointestintal disturbances, and cognitive impairment. Investigations have shown heightened inflammatory markers both peripherally and centrally in those diagnosed with Gulf War Illness.

inflammatory biomarkers such as elevated levels of pro-inflammatory cytokines, IL-1β, INF-γ, or IL-6 (12, 13) have been found in the serum of GWI patients. Increased concentrations of inflammatory cytokines are also associated with different mood disorders, including bipolar and major depressive disorders (14, 15). Dysfunction of the innate immune system might be behind the depressive behavior observed in veterans with GWI.

To date, only incremental progress has been made towards the creation of a therapeutic for GWI; there is no FDA approved therapy. In 2008, following the publication of the findings of the Research Advisory Committee on Gulf War Veterans' Illness, it was determined that the top priority in the next phase of GWI research should be the identification of a treatment (2). A putative strategy for developing novel therapeutics to treat GWI may leverage the many shared neuroinflammatory pathologies of mood disorders and GWI (9, 16). In this review, we discuss the relationship between the innate immune system, exposure to environmental toxins, and the resultant neuroinflammation leading to the development of Gulf War Illness. Furthermore, we propose that the pathomechanisms by which Gulf War Illness occurs possesses significant overlap with those found in many mood disorders, leading to a larger than expected concomitant rate of diagnosis in individuals with Gulf War Illness. Understanding this complex relationship may provide the opportunity to develop novel therapeutic strategies as well as a method to prevent similar disease.

## INNATE IMMUNITY

The immune system's response to an insult can be broken down into two overarching arms: the specifically responding adaptive immune system and the nonspecific innate immune system. Adaptive immunity is slow; to mount a response against previously encountered antigens, specific B, and T cell colonies are activated and grow to defend the host. In contrast, innate immune responses rapidly act to combat threats (17). This rapidity is essential and enables the body to act *via* nonspecific action while a targeted response by the adaptive immune system is prepared. An integral way in which the innate immune system participates in cellular defense is through the activation of various receptors and sensors to activate caspase-1, and subsequently induce an inflammatory response mediated by pro-inflammatory cytokines, such as IL-1β or IL-18, among others (18). In the central nervous system, the main innate immune cells of the brain, microglia, participate in the nonspecific innate immune response, driving neuroinflammation (19). Microglial mediated neuroinflammation is of particular interest in the pathology of GWI and has been recently demonstrated with *in vivo* PET imaging in individuals diagnosed with GWI. Individuals diagnosed with GWI demonstrated a heightened signal of TSPO, a marker of microglial activation. TSPO signal was found to be significantly elevated in cortical regions including the precuneus, prefrontal cortex, and the primary motor and somatosensory cortices (11). This direct evidence of neuroinflammation in individuals diagnosed with GWI underlies the importance of research into the mechanisms by which GWI toxins activate the innate immune system, causing lasting neuroinflammation.

### Inflammasome Assembly and Activation in Response to GWI Toxins

Instrumental in the response of the innate immune system are inflammasomes: multiprotein complexes which assemble upon response to either an exogenous or endogenous insult. Components of the multiprotein complex include a pattern recognition receptor (PRR) protein, which may exist on the cell membrane or intracellularly, an adaptor protein, and an effector (20). One of the best characterized inflammasomes is the NOD-, LRR-, and pyrin domain containing protein 3 (NLRP3) complex, which plays an essential role in the initiation and propagation of the innate immune response. In the central nervous system, *Nlrp3* is highly expressed in microglia (21). The end result of activation of the NLRP3 inflammasome in microglia is the release of pro-inflammatory cytokines IL-1β and IL-18 (**Figure 2**).

The induction of the innate immune system by NLRP3 occurs in a two-step process, priming, and activation, in response to either an endogenous or exogenous insult. Externally derived threats are termed pathogen associated molecular patterns (PAMPs) and include bacterial endotoxins and glycoproteins. Those that originate from within the host are danger associated molecular patterns (DAMP) and include metabolites of purines, nucleic acids, reactive oxygen species, and heat shock proteins (22).

The ability of inflammasomes to respond to these DAMPs, often released during periods of extreme stress or toxicity, are a central tenant to the role of inflammasomes in the pathogenesis of GWI. DAMPs have been implicated in the development of neuroinflammation in both *in vitro* and *in vivo* animal models of GWI, with exposure of GWI associated chemicals leading to increases in various DAMPs, including the HMGB1 (23). The initial priming step is the result of the binding of a PAMP or DAMP to a PRR. The binding of the exogenous molecule lipopolysaccharide (LPS) or various endogenous molecules produced due to tissue injury such as high-mobility group box 1 protein (HMGB1) can result in the activation of the toll-like receptor 4 (TLR4)/NF-κB pathway. Under normal conditions, HMGB1 exists as a ubiquitous nuclear DNA binding protein, but during periods of cellular stress such as excitotoxicity, necrotic conditions, or traumatic brain injury, HMGB1 is released from neurons and astrocytes into the extracellular space and binds to the TLR complex of microglia, activating the transcription factor NF-κB. NF-κB activation leads to the transcription of zymogenic *pro-IL-1β* as well as the upregulation of *Nlrp3* (24, 25).

Following the priming step, the NLRP3 inflammasome may be activated, the induction of which can occur by various signals. A detailed mechanism for the activation step of inflammasome activity has not been elucidated in entirety, however various models have been put forward. Ion fluxes, such as those from $K^+$, $Ca^{2+}$, $Na^+$, and $Cl^-$) have been proposed to participate (26). For example, in the presence of damaged cells, a high concentration

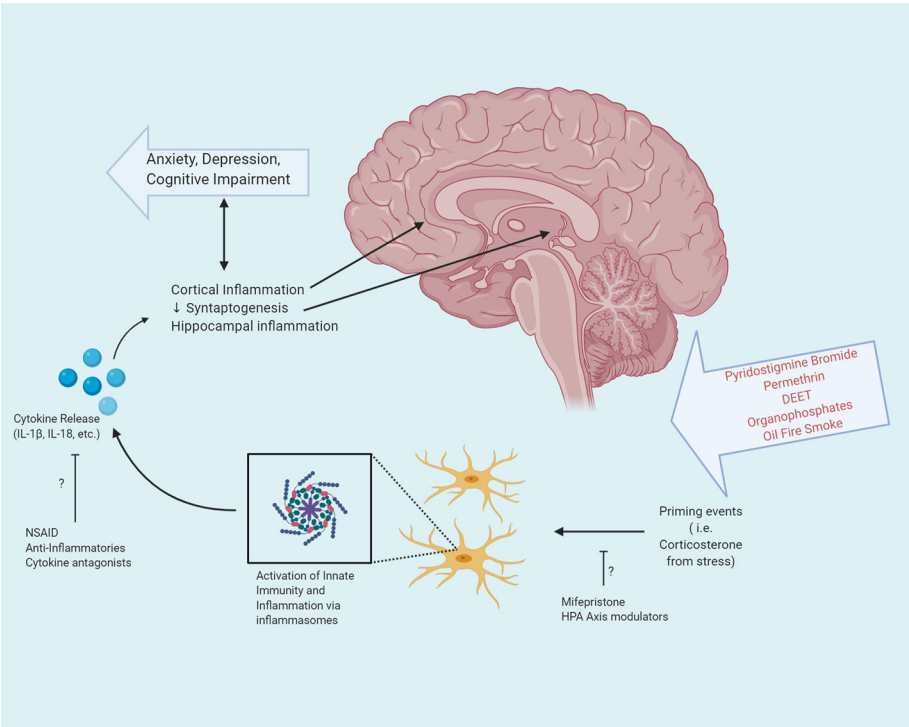


**FIGURE 2 |** Exposure to the various neurotoxicants encountered during the Gulf War, in combination with prolonged stress can activate the innate immune system *via* inflammasomes. Activation of inflammasomes in microglia in the central nervous system results in the release of pro-inflammatory cytokines. These cytokines exert pleiotropic effects based upon their target destination and can result in both cortical and hippocampal inflammation, as well as decreased synaptogenesis, leading to anxiety, depression, and cognitive impairment. Potential therapeutic interventions may target the step of priming events or cytokine release, to attenuate or prevent the inflammatory cascade resulting in GWI.

of extracellular ATP is often present. This high concentration induces the purine receptor P2X7 to open, allowing potassium to be released, the ionic effects of which are counteracted by calcium influx (27). The molecular mechanism by which these ion fluxes contribute to the release of pro-inflammatory cytokines are not fully known; however various *in vivo* models in which knock-out P2X7 mice were challenged with LPS, demonstrated significantly decreased secretion of IL-1β (28).

In response to activation, the innate immune cells rely on inflammatory cytokines from the TNF and Interleukin-1 family. A major participator in the inflammatory cascade is the pro-inflammatory cytokine, IL-1β. Once secreted, IL-1β exerts its inflammatory effects through binding to IL-1 receptors in the microenvironment and promoting the expression of cyclooxygenase-2 (*Cox-2*), phospholipase A2 (*Pla2*), and inducible nitric oxide synthase (*iNos*) of microglia and monocytes, each of which further participates in the inflammatory cascade. IL-1β also has the capability to increase the expression of adhesion molecules such as intercellular adhesion molecule-1 (ICAM1) on mesenchymal cells and vascular cell adhesion molecule-1 (VCAM1) on endothelial cells, functioning to increase adhesion and retention of immune cells to their target tissue (29).

In the brain, IL-1β exerts pleiotropic effects based upon cell type. In microglia and astrocytes, the binding of IL-1β to the IL-1 receptor leads to the activation of the NF-κB pathway. However, when bound to the IL-1 receptor of hippocampal neurons, rather than activating the NF-κB pathway, inflammatory levels of IL-1β activates the MAPK and CREB pathway thereby modulating synaptic strength and long-term potentiation. Interestingly, the effects of IL-1β in hippocampal neurons exhibits a dose-dependent response: low concentrations of IL-1β promote long-term potentiation and the formation of memories, whereas at elevated levels, a decrease in LTP and memory consolidation is noted (30). As memory deficits are disproportionately observed clinically in individuals with GWI, the effects of elevated levels of IL-1β in the hippocampus may be of particular interest in elucidating the pathophysiology of the disorder (31) (**Figure 2**). Neuroimaging in GWV with confirmed exposure to organophosphates reveals reduced volume of the CA2 and CA3/Dentate Gyrus subfields of the hippocampus (32, 33). Furthermore, elevated levels of IL-1β have been demonstrated *in vivo* in the hippocampus of animals in models of GWI (34). The association of IL-1β concentrations in hippocampal neurons may putatively serve as a target for therapeutic intervention.

## Sensitization of the Innate Immune System

The magnitude of inflammatory proteins released by microglia is plastic; rather than an all or nothing release, microglia are able to dynamically modulate their release of cytokines. Previous exposure of microglia to an insult can either increase or decrease the sensitivity and subsequent reactivity *via* the release of proinflammatory cytokines upon secondary exposure to an event (35). Demonstrated *in vivo*, when given an initial subthreshold dose of LPS, mice manifest regular, non-increased levels of IL-1β in the CNS. However, when a second dose of LPS is administered 24 h after the initial, elevated levels of IL-1β, TNF-α, and IL-12 were demonstrated in the CNS, despite an attenuation of the production of cytokines by the cells of the periphery (36). This sensitization provides valuable insight into the pathogenesis of various diseases, in which repeated exposure to subthreshold stressors may ultimately elicit a full, or even heightened response.

Subthreshold levels of cytoplasmic NLRP3 protein prevent the catalytic reaction of pro-interleukins from occurring. In chronic diseases with inflammatory components, upregulation of *Nlrp3* mRNA has been demonstrated including chronic periodontitis and diabetes mellitus (37). Mutations in the NLRP3 gene possess clinical relevancy in humans; when occurring in the capsase-1 domain of NLRP3, affected individuals exhibit uncontrolled excretion of IL-1β and IL-18 as part of the autoimmune disorder Muckle-Wells Syndrome, presenting with arthralgia, fatigue, and dermatological pathology (38).

Corticosterone, a glucocorticoid synthesized and secreted by the adrenal cortex during prolonged periods of stress, has been proposed to play a contributory role in the priming step of the innate immune system (39). Corticosterone has been shown to increase the basal level of mRNA expression of several proteins found in the NLRP3 inflammasome complex (40). This effect has been demonstrated both *in vitro* and *in vivo*; in primary macrophages derived from both human and mice, the treatment of cells with glucocorticoids was found to rapidly induce expression of *Nlrp3*. Furthermore, when these cells were assayed for IL-1β secretion, it was demonstrated that the administration of glucocorticoids greatly increased levels of mature IL-1β released (41). To investigate the effects of glucocorticoids on inflammasome priming *in vivo*, studies have been conducted administering methamphetamine, a potent mediator of neuroinflammation. Mice chronically pretreated with corticosterone, in a paradigm designed to mimic the physiological effects of prolonged stress, and subsequently administered methamphetamine, demonstrated significant increases in TNF-α, CCL-2, LIF, and IL-1β compared to animals given a single pretreatment dose of corticosterone prior to methamphetamine treatment (42). This exaggerated immune response induced by the chronic administration of corticosterone prior to the inflammatory insult also coincided with physiological abnormalities such as substantially increased dopaminergic cell death and increased numbers of activated microglia.

## GW Toxins and Innate Immunity

The neuroinflammation observed in individuals with GWI has been recapitulated both *in vivo* and *in vitro* as a result of the toxic exposure to the various chemicals encountered by deployed GWV. Interestingly, models have also investigated the contributory effects of sustained levels of physiological stress, which may serve a role in the sustained activation of microglia. Below we review various animal models of GWI and their key findings as they relate to the pathogenesis of neuroinflammation and systemic inflammation (**Figure 1**).

Permethrin (PER) is a type I pyrethroid insecticide which acts on voltage gated Na+ channels in neurons to produce a long chain of action potentials following a single stimulus (43). This insecticide is one of the many environmental exposures experienced by veterans of the first gulf war (2). Permethrin has been shown to act on voltage gated sodium channels present on microglia and stimulate the release of TNF-α in a dose and time dependent manner (44).

Numerous *in vivo* studies have reported increases in inflammatory markers after chronic exposure to permethrin when co-exposed with various combinations of PER, pyridostigmine bromide (PB), N, N-Diethyl-meta-toluamide (DEET), and/or chronic stress. Carreras and colleagues demonstrated that chronic exposure to PER, PB, and DEET, along with 5 min of restraint stress for 28 days produced a significant increase in the number of activated microglia in CA1-3 regions of the hippocampus in mice at time point of 3 months post-exposure. Interestingly, these findings were accompanied by increased anxiety-like behavior in an elevated plus maze behavioral test (45).

Chronic 10-day administration of PB and PER in the absence of chronic stress has been shown to increase inflammation, as detected by increases in the phosphorylation of NF-κB and STAT3 and corresponding increases in IL-1β, IL-6, and IFN-γ in the brains of mice 11 months post-exposure. IL-1β and IFN-γ were also elevated in the plasma taken from these mice. Animals in this study were also evaluated for fatigue and anxiety behaviors. At 3 months post-exposure the animals showed an increase in the amount of time spent immobile in a forced swim test, a finding suggested to mirror increases in fatigue and depression commonly observed in GWI patients. Additionally, the mice in this study were found to display disinhibition behavior as measured by an increased amount of time in the open arms of an elevated plus maze (46). While the reason for differences in elevated plus maze behavior between the studies by Carreras and colleagues and Joshi et al. has not been explicitly studied, it is likely a result of differences in the experimental protocols (i.e. use of chronic restraint stress and DEET).

An *in vivo* model of GWI demonstrated the ability of the toxins encountered during the Gulf War, pyridostigmine bromide and permethrin, with subsequent administration of corticosterone to stimulate stressful conditions, to activate the NLRP3 inflammasome in enteric glial cells. Rodents treated with pyridostigmine bromide and permethrin followed by corticosterone exhibited activation of TLR4 receptors and an

upregulation in expression of *Nox2*- a producer of super-oxide, ultimately leading to the activation of the NLRP3 inflammasome, as well as upregulation of mRNA for *Nlrp3*, *Caspase-1*, and *Il-1β* (47).

While multiple animal models of GWI have been used, neuroinflammation remains a prominent feature across various combinations of Gulf War toxins and stressors. A recent study compared two models of GWI, PB+PER (Model 1) and PB+DEET+CORT+DFP (Model 2). Animals in Model 1 received treatment with PB and PER concurrently for 10 days; Model 2 animals received treatment with PB and DEET for 14 days, with administration of CORT on days 8–14 and a single dose of DFP on day 15. The authors showed increased expression of IL-1β, CCL-2, *Casp1*, and a trending increase in *Tnf*-α in the ventral hippocampus of mice in both models, with stronger increases seen in Model 2. Interestingly, *Hmgb1* showed a trending increase (34).

Research regarding the gut-brain-axis has received growing attention and excitement in recent years and may represent a potential mechanistic explanation for GWI. Seth and colleagues demonstrated that oral administration of PER+PB was associated with dysregulation of both the gut virome and bacteriome in mice leading to a weakening of tight junctions in the GI, as well as systemic inflammation, neuroinflammation and decreased BDNF expression in the frontal cortex. Interestingly, these mice displayed increased levels of the pro-inflammatory cytokine IL-6 in the frontal cortex. IL-6 levels in PER+PB treated mice could be reduced by treatment with antibiotic and antiviral compounds, a finding that suggests gut dysbiosis and bacteria-virus communication could be factors in neuroinflammation observed in GWI models (48).

O' Callaghan and colleagues demonstrated that exposure to the sarin surrogate Diisopropyl fluorophosphate (DFP) produces neuroinflammatory effects, as measured by increases in several cytokines across multiple brain regions. Interestingly, increases in TNF-α, IL-1β, and OSM were further enhanced by prior administration of CORT to mimic physiological stress. Administration of PB and DEET did not enhance DFP-induced neuroinflammation, or produce neuroinflammation outright (49). A subsequent study compared the ability of various cholinesterase inhibitors to stimulate neuroinflammation with or without the prior administration of CORT. The study compared two organophosphate irreversible AchE inhibitors and two carbamate reversible AchE inhibitors. The organophosphates used in the study were DFP and Chlorpirifos-Oxon (CPO). Chlorpirifos-Oxon is the active metabolite of Chlorpirifos, an insecticide used in the first gulf war. The carbamates used in the study were PB and physostigmine (PHY). Physostigmine is a carbamate similar to PB, but with the ability to penetrate the blood-brain-barrier. Both DFP and CPO stimulated a robust increase in the levels of several inflammatory cytokines in the cortex and hippocampus of mice with corresponding activation of the downstream neuroinflammatory signaling effector STAT3, in a manner which could be exacerbated by prior treatment with CORT. The same neuroinflammatory effect was not observed with PB or PHY (50). A follow-up study looking at exposure to DFP, CPO or PHY alone or in combination with CORT found elevations (or lack thereof) of cytokines in various brain regions did not readily correlate with region specific changes in Ach from the various treatments. These results were interpreted to suggest that off target (non-AchE) actions of OPs may be chiefly responsible for the observed changes in neuroinflammation (51). An additional study from the same group demonstrated that the observed neuroinflammatory effects of DFP+CORT in mice extend to rats as well and are accompanied by changes in microdiffusivity as detected by MRI (52). A recent study using RNAseq analysis found 32 genes that were differentially expressed in both the cortex and hippocampus of mice treated using the same DFP+CORT exposure regime mentioned above. In particular these changes in gene expression were associated with functions such as cytokine-cytokine receptor interactions, regulation of chemokine production, and regulation of I-κB kinase/NF-κB signalling (53). Finally, it has also been observed that the neuroinflammatory changes resulting from GWI toxin exposures are not mirrored in the periphery. For example DFP alone elevated mRNA expression of several proinflammatory cytokines in the liver as had previously been reported in the brain (49), but chronic CORT exposure suppressed these changes in contrast to what had previously been observed in the brain. A similar pattern of DFP induced inflammation suppressed by CORT was also observed in the serum. The study also looked at PB+DEET exposure and found this treatment had no or reduced effect on mRNA expression of cytokines in the liver. Exposure to CORT with or without PB+DEET was associated with reductions in serum cytokine expression. Exposure to PB+DEET was associated with no or reduced expression of most proinflammatory cytokines in the serum. It should be noted however, that PB+DEET exposure did increase concentrations of IL-1α, IL-6, and IL-2 in the serum at some of the time points evaluated (2 and 72 h, 12 h, and 6 and 12 h, respectively) (10).

Autoimmunity may also play a role in the pathogenesis of GWI. A recent study examined the contributions of adaptive immune response in a PER + PB model of GWI. The PER metabolite 3-PBA was shown to haptenate albumin, and autoantibodies against 3-PBA-albumin were detected in the plasma of mice chronically exposed to PER+PB, as well as GWI patients and farm workers exposed to pyrethroid insecticides. 3-PBA-albumin was also shown to activate CD4+ T-helper and antigen responsive B-cells in ex vivo murine blood. These immune cells were also shown to be elevated in PER+PB exposed mice as well as GWI patients. Interestingly, the authors also reported an increase in infiltrating monocytes in the brains of mice chronically exposed to PER+PB. Additional evidence for a potential autoimmune component of GWI is supported by the detection of antibodies against a number of CNS proteins in GWI veterans as well as agricultural workers exposed to organophosphates. In particular autoantibodies against GFAP, Tau, MAP2, and myelin basic protein (MBP) were detected (54, 55).

Further interplay of the innate and adaptive arms of the immune systems have been hypothesized to contribute to the pathogenesis of GWI. Bridging the innate and adaptive immune systems is the process of antigen presentation, by various cells,

including the macrophages of the innate immune system (56). In the process of antigen presentation, macrophages upregulate major histocompatibility complex class II (MHC Class II) to present to $CD4^+$ T cells (57). Human leukocyte antigen (HLA) Class I, II, and III genes are transcribed from the MHC region of human chromosome 6. Dysfunction in HLA Class II genes have previously been demonstrated in Veterans with GWI and hypothesized to confer susceptibility to the myriad of environmental insults and exposures encountered during deployment. Interestingly, GWV deployed during this time with higher allelic frequency of HLA genes may provide protection from the development of GWI (58).

## RELATIONSHIP BETWEEN INFLAMMATION, INNATE IMMUNITY AND MOOD DISORDERS

Among the constellation of symptoms and illnesses present in GWI is a high rate of diagnosis of a concomitant mood disorder; interestingly, those with a comorbid mood disorder diagnosis exhibit increased severity of symptoms (59). In fact, among the multi-pronged diagnostic criteria as outlined by the Kansas definition of GWI, is cognition/mood impairments, fatigue, pain, respiratory dysfunction, and GI or dermatologic symptoms (60).

Various mood and psychiatric disorders were found to occur at a higher than expected level in deployed GWV when compared to non-deployed GWV. In addition, meta-analysis of 14 studies of GWV determined that there was greater than twice the odds ratio of developing depression compared to military personnel non-deployed during the Gulf War (61).

Considering this degree of concomitant diagnosis and many shared neuroinflammatory pathologies, we describe below a number of key neuroinflammatory findings of various neuropsychiatric disorders which may explain this concurrence.

One dilemma that must be addressed is the direction of causality of inflammation in psychiatric disorders; is inflammation the cause, or does it solely represent a symptom of underlying features of neurological dysfunction such as synaptic malformation, improper neurite outgrowth, or neurotransmitter dysfunction? The first shred of evidence about the relationship between pro-inflammatory cytokines and mood disorders was reported in 1991 by Smith (62). In this study, the administration of monokines to volunteers increased the rate of depressive disorders, which agreed with the higher prevalence of depression in patients with inflammatory conditions, such as rheumatoid arthritis. From then, different studies have shown that inflammation not only coincides with psychiatric disorders but that it also exacerbates the symptom severity in several syndromes. The impact of pro-inflammatory cytokines has been mostly studied in major depression disorders (MDD). In a meta-analysis of studies conducted by Dowlati *et al.*, cytokine levels in patients with MDD were analyzed, and it was concluded that depression coincides with alterations of the inflammatory response system (63). Nevertheless, enhanced cytokine levels are also found in other psychological conditions, such as bipolar disorder (BPD) (64, 65), anorexia nervosa (66), panic and posttraumatic stress disorders (67), schizophrenia (68), and even neurodegenerative conditions including Alzheimer's disease (69). When analyzing the causative relationship between cytokines alterations and psychiatric illnesses, a retrospective study of 3 million medical records in the Netherlands concluded that a history of hospitalization for infection was associated with an increased risk of later developing a mood disorder, including depression and bipolar disorder (70). Interestingly, chronic inflammation also seems to promote addictive behaviors. In a study that analyzed the genomic DNA isolated from 60 opioid-dependent, 99 alcohol-dependent patients, and 60 healthy nondependent controls, demonstrated that single nucleotide polymorphisms in the IL-1β gene was related to alcohol and opioids-dependency (71).

Shifting the focus toward the concentration of specific inflammatory proteins in neuropsychiatric patients, clinical studies found a significant augmentation in the concentration of IL-18 in patients with MDD panic disorder (72), and increased levels of IL-1β in depression and bipolar disorders (73), while TNF-α seems to mediate the production of anorexigenic peptides in anorexia nervosa (74). A meta-analysis about MDD published in 2012, which included 29 studies of the proinflammatory cytokines in the serum of 1548 patients––822 MDD, 726 healthy controls—confirmed that soluble IL-2 receptor, IL-6, and TNF-α levels are increased in MDD (trait markers), while, IL-1β, IL-2, IL-4, IL-8, and IL-10, are not statistically different from controls (63). A recent review summarizes alterations in serum cytokines in BPD; TNF-α, IL-6, and IL-8 are elevated during manic and depressive phases, whereas IL-2, IL-4, and IL-6 are increased during mania (75). Two more studies reported that IL-1β and IL-1 receptor serum levels of MDD, BPD, and schizophrenia patients are not statistically different from those of healthy controls (14), although tissue studies revealed increased levels of IL-1β and IL-1 receptor in the frontal cortex of BPD patients (76).

The relationship between mood disorders and inflammation has also been extensively studied in the laboratory, using both *ex vivo* cultures from depressed patients and animal models. For instance, olfactory bulbectomized rats present neuroendocrine, behavioral, and immune modifications similar to those found in MDD patients, which might be related to alterations of the inflammation-HPA axis, and inflammation-nerve growth factor-memory pathway (77). Several works using rat and mouse models of stress have demonstrated the influence of inflammatory cytokines in stress-induced depressive cases. Thus, mice subjected to chronic-mild stress present different symptoms of depression, including adrenocortical activation, decreased neurogenesis and behavioral alterations, as a consequence of elevated IL-1 levels in the brain (78) (For putative illustration of neuroimmune interactions and GWI pathogenesis see **Figure 2**). Acute immobilization stress-induced in rats increased levels of IL-1β and TNF-α, which correlated with depressive behaviors and impaired neurogenesis

(79). Another animal model that explores the interaction between the immune system and mood alterations is administration of bacterial lipopolysaccharide (LPS). In rodents, intraperitoneal LPS injection promotes altered behaviors related to anxiety and depression, such as reduced social behavior, anhedonia, or decreased libido (78, 80, 81). These changes are associated with augmented concentrations of IL-1 (α and β), IL-6, and TNF-α (82). Furthermore, peripheral blood mononuclear cells (PBMC) cultures from schizophrenic patients produced higher concentrations of IL-18 and IL-1β, both spontaneously and upon stimulation with LPS (83).

## TARGETING INFLAMMATION IN MOOD DISORDERS AND GWI: A COMMON MECHANISM

Targeting the process of priming in neuroinflammation may yield novel treatment strategies to both treat, as well as prevent the pathogenesis of diseases with a chronic inflammation component, such as GWI or various neuropsychiatric disorders. As many psychiatric disorders display a number of commonalities with regards to neuroinflammation and GWI, there exists a potential area of overlap for which treatments may be effective. Described below are a selection of therapeutics targeting inflammation that have been trialed either in Gulf War Illness or in disorders shown to have similar neuroinflammatory effects.

Neuronal inflammation frequently coincides with psychiatric disorders such as MDD, BPD, or schizophrenia. Thus, the most obvious question that arises is whether anti-inflammatory drugs are useful for the treatment of these diseases. Several studies attempted to treat psychiatric disorders with different types of approved anti-inflammatory drugs; however, there are important inconsistencies about the effectiveness of the studied drugs. Four major categories of anti-inflammatory drugs have been typically evaluated; non-steroidal anti-inflammatory drugs (NSAIDs), polyunsaturated fatty acids (PUFAs), and cytokines inhibitors, and the antibiotic minocycline (84–86). NSAIDs are a group of anti-inflammatory drugs that inhibit cyclooxygenase (COX) enzymes, blocking the synthesis of prostaglandins. There are several NSAIDs available with different commercial names and specificity for COX-1 and COX-2. PUFAs are a family of long-chain n-3 polyunsaturated fatty acids that exert anti-inflammatory effects by reducing the expression of inflammatory genes, probably through targeting the NF-κB pathway (87). Cytokine inhibitors include nonpeptidic molecules that suppress cytokine synthesis, soluble receptors that sequestrate the synthesized cytokines, and autoantibodies that neutralize complement-mediated cell death (88). Among this latest group, anti-TNF-α drugs deserve particular attention. Finally, minocycline is a second-generation tetracycline antibiotic that presents anti-inflammatory properties independent from its anti-bacterial effect.

In 2014, Köhler et al. published a meta-analysis based on 14 studies from randomized clinical trials, and 6262 patients with depressive symptoms, or MDD. They concluded that the treatment with anti-inflammatory drugs (specifically, both cyclooxygenase-2 inhibitors and anti-cytokine therapies) reduced depressive symptoms. However, there was considerable heterogeneity among the conclusions reached by the studies included in the meta-analysis (89). Another extensive qualitative review evaluated the effectiveness of the four types of anti-inflammatory drugs as add-on therapies for BPD, MDD, and schizophrenia (85). This study inferred that PUFAs improved symptoms of MDD patients, although the beneficial effects depended on the eicosapentaenoic acid content of their diet (90). There was no evidence of improvement in schizophrenic patients treated with PUFAs (91), while there were mixed results for subjects with bipolar disorders (92). Regarding the use of NSAID, the cyclooxygenase-2 inhibitor effectively improved the symptomatology of depressed patients, having a more modest impact on schizophrenia and no effect at all on BPD. The anti-TNFα drug Infliximab has been tested in MDD patients resistant to other anti-depressants. In general, the drug did not improve the symptoms of the disease, and only those patients with a high baseline of inflammatory biomarkers (>5 g/l of the high-sensitivity C-reactive protein), showed some improvement. In this subgroup of individuals, Infliximab administration ameliorated anhedonia, anxiety, depressed mood, and suicidal thoughts (93). No anti-TNFα therapies have been tested in BPD and schizophrenic patients. There are limited data regarding the use of minocycline to treat psychiatric disorders; however, the administration of the antibiotic as an add-on to the conventional therapies improved the symptoms of MDD and schizophrenic patients (94, 95).

Antidepressant medications have been additionally investigated for their anti-inflammatory capacities. Hannestad *et al.* in a meta-analysis published in 2011 in Nature Neuropsychopharmacology, analyzed the effect of antidepressant drugs in the serum levels of inflammatory cytokines, including TNFα, IL-1β, and IL-6 (96). Patients diagnosed with MDD and treated with approved medicines for depression presented lower serum levels of IL-1β than before the treatment. However, the reduction of the IL-6 concentration was less clear, and TNF-α levels remained unaltered. Interestingly, when subgrouping the data according to the class of antidepressant, serotonin reuptake inhibitors significantly reduced IL-6 and TNF-α levels, while other antidepressants did not alter these proinflammatory markers (96). Partially contrasting with this study, another meta-analysis published in 2018, concluded that the use of antidepressant for the treatment of MDD reduced IL-4, IL-6, and IL-10, while the drugs did not significantly change IL-2, TNF-α, IFN-γ, or CRP. According to this study, IL-1β was only reduced by serotonin reuptake inhibitors, whereas other types of antidepressants did not affect this cytokine (97). Nevertheless, both studies agreed about the higher levels of inflammatory cytokines found in MDD patients, which could contribute to depressive symptoms.

The heterogeneous response found among individuals evinces the necessity to characterize the inflammatory profiles of psychiatric patients to provide personalized and more effective therapy.

## THERAPEUTIC STRATEGIES IN GULF WAR ILLNESS

There is currently no standard FDA approved therapy used for the treatment of GWI. In fact, the Research Advisory Committee on Gulf War Veterans' Illnesses has designated the identification of effective treatments for GWI as the highest priority in GWI research (2). ClincialTrials.gov currently lists 52 different clinical studies examining a number of different therapeutic interventions for GWI. However, very few of the listed studies have successfully reached completion and published their results. Several studies involving non-pharmacological interventions (i.e. acupuncture, cognitive behavioral therapy) and nutritional supplementation studies have been performed in patients with GWI (98). For the purposes of the present review the focus will remain solely on nutritional and pharmacological agents tested in rodent models as well as symptomatic GWV.

### Coenzyme Q10

Coenzyme Q10 (CoQ10) is concentrated mainly in the mitochondria and is integral in energy production (99). Recent evidence also suggests that CoQ10 can also serve as an antioxidant by protecting the cell membrane from reactive oxygen species (ROS). As ROS have been hypothesized to play a contributing role in the pathogenesis of GWI, as well as numerous psychiatric conditions, CoQ10 has been trialed as a treatment for GWI (100, 101). In randomized, double-blind, placebo-controlled study of individuals diagnosed with GWI, participants were administered CoQ10 at either 100 mg a day, 300 mg a day, or as a placebo for 3.5 months. Individuals treated with 100 mg of CoQ10 daily reported significant improvements in General Self-Reported Health compared to baseline; however this effect was limited only to male participants. In an objective measure of physical function, improvements in individuals in the 100 mg group were significantly increased compared to placebo, with the effect present in both male and female participants (102).

### Mifepristone

A randomized double-blind cross-over trial was conducted in Gulf War Veterans with diagnosed chronic multi-symptom illness using the type II glucocorticoid receptor antagonist mifepristone. Subjects received 200 mg/day for 6 weeks and were assessed across a battery of cognitive tests. Treatment was associated with significant improvements in verbal learning. However, mifepristone was not associated with improvements in working memory, visual learning, or on the overall composite score. Treatment was also associated with increased levels of plasma cortisol and ACTH, as would be expected from chronic GR antagonist administration (103).

### Doxycycline

One of the less common theories surrounding GWI is that underlying systemic infection with Mycoplasma may be a causal factor in the disorder. Based on this hypothesis a randomized, double-blind, placebo-controlled clinical trial was conducted in GWI patients with detectable Mycoplasma DNA in their blood. The treatment used in the study was 200mg per day of Doxycycline over a period of 12 months. The study failed to find any improvement in the primary outcome measure of physical health function after 12 months. Additionally the study found no significant differences in pain, fatigue, cognitive symptoms, and mental health following 12 months treatment (104).

### Potential Future Directions

Various medications currently FDA approved may hold potential in being trialed in cases of GWI. Suramin, a medication previously used in the treatment of African Trypanosomiasis, can act a non-selective inhibitor of purinergic signaling and may have efficacy in attenuating the activation step of NLRP3 activity by blocking the P2x7 receptor. Interestingly, Suramin has recently been trialed in Phase I/II, low dosages as a treatment for Autism Spectrum Disorders to determine safety. While the study was unable to draw robust statistical conclusions regarding the efficacy of Suramin as a treatment, modest improvements in ASD symptomology were present in individual in the experimental group (105). As purines serve as a DAMP for inflammasome activation, the use of Suramin may be of interest as a potential treatment in GWI.

Anakinra, an interleukin-1 receptor antagonist (IL-1Ra) is currently FDA approved for the treatment of rheumatoid arthritis (106). In addition to the currently approved indication, Anakinra has been trialed in a number of other conditions with inflammatory components, including stroke and ALS, although there have been varying degrees of success regarding changes in clinical outcomes and changes in serum levels of inflammatory cytokines (107). Although varying efficacy has been demonstrated, the safety profile, dearth of approved GWI treatments, and heightened levels of IL-1β found in GWI may warrant further trials.

### Rodent Studies

Joshi and colleagues demonstrated that the Peroxisome proliferator-activated receptor alpha (PPAR-α) agonist Oleoylethanolamide (OEA) was sufficient to reverse cognitive deficits in the Barnes maze in a mouse model of GWI (PB+PER). OEA treatment was also able to reverse PB+PER induced depressive and disinhibition behaviors as measured *via* forced swim test and elevated plus maze. OEA treatment was also found to effectively reverse PB+PER stimulated increases in the phosphorylation of the NF-κB subunit p65, as well as STAT3 phosphorylation. OEA was also effective in reversing PB+PER stimulated increases in the levels of IL-1β, IL-6, and IFN-γ (46). OEA is an endogenous acylethanolamide with known anti-inflammatory actions. The exact mechanism of anti-inflammatory action by OEA is currently unknown however several mechanisms have been proposed such as the alterations in inflammatory signaling pathways and genes down stream of various receptors known to be targeted by acylethanolamides such as CB receptors, PPARs, and TRPVs (108).

The antibiotic minocycline has anti-inflammatory actions and has been shown to be effective in preventing CORT+DFP induced increases in inflammatory cytokine expression. Co-treatment of minocycline with CORT+DFP was associated

with decreases in the expression of TNF-α, CCL2, IL-1β, LIF, and OSM in the frontal cortex and hippocampus of treated mice (49). Minocycline is a tetracycline antibiotic which has been shown to be neuroprotective, immunomodulatory, and anti-inflammatory in a number of different animal models. Some of the proposed mechanisms for these additional effects include inhibition of iNOS, MMPs, and $PLA_2$. As well as inhibition of caspases-1 and -3 and inhibition of PARP-1 (109).

A study by Seth and colleagues (see above section *GW toxins and innate immunity*) tested co-exposure with antibiotics (Neomycin + Enrofloxacin) or the antiviral compound Ribavirn in conjunction with PB+PER. The study showed that treatment with Ribavirn resulted in a gut viral composition that was similar to control mice that were not exposed to PB+Per, a result not found with the antibiotic treatment. Antibiotic treatment was associated with preventing changes in gut bacteria diversity that occurred with PB +PER exposure, whereas antiviral treatment was not. Interestingly, both antibiotic as well as antiviral therapy were associated with prevention of increases in serum IFNγ and IL6 after exposure to PB +PER (48). While antibiotic therapy has previously been tested in symptomatic Gulf War Veterans without success, the strategy of deliberately altering gut microbiome composition has not yet been tested in GWI patients.

In addition to pharmaceuticals, natural phytochemicals have also been trialed *in vivo* as treatments for the neuroinflammation present in GWI. One such natural supplement, curcumin, has been demonstrated to have potent anti-inflammatory and anti-oxidant effects *via* its action through a number of pathways, including the NF-κB and STAT3 signaling paths (110). At 9 weeks of age, male rats were exposed daily to DEET, permethrin, and pyridostigmine bromide, plus physical restraint for a period of 28 days. Animals were subsequently administered curcumin daily or a vehicle injection. Animals exposed to GW toxins and treated with curcumin exhibited improved cognitive and mood function, hippocampal neurogenesis, and reduced hippocampal inflammation, when compared to vehicle treated, GW toxin exposed (111). Demonstrated *in vivo* efficacy of curcumin to attenuate neuroinflammation sequelae of GWI suggests further preclinical and clinical trials are warranted.

## CONCLUSION

With the high incidence of GWI in deployed GWV and a current lack of approved treatment, there exists a need for new trials targeting novel mechanisms. Neuroinflammation as catalyzed by the innate immune system represents a major contributor to the pathogenesis of GWI, along with the concurrence of concomitant mood disorders. Future therapeutic strategies that leverage the commonalities in these pathomechanisms may yield promising developments in creating a treatment. Furthermore, GWI has a high degree of overlap with the fields of environmental toxicology, psychiatry, immunology, and neurology; an interdisciplinary effort across multiple fields is essential for a better understanding of its underlying mechanism. Interdisciplinary research may also provide important contributions to each of these respective fields. The development of therapeutics for the treatment of GWI may potentially be repurposed for treating other disorders, highlighting the continued value in pursuing both mechanistic and therapeutic driven studies.

## AUTHOR CONTRIBUTIONS

All authors contributed to the conceptualization, writing, and editing of this manuscript.

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REVIEW
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# From the Frontline to the Homefront: The Experience of Israeli Veterans

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In 1948, the state of Israel was created as a homeland for the Jewish people after 2,000 years of persecution and deportations in the diaspora. During the past 72 years, its inhabitants have experienced several wars and numerous terrorist attacks. Therefore, the issue of trauma goes beyond academic study, it is part of daily life. These circumstances have, unfortunately, turned Israel into a natural stress laboratory, which has enabled the systematic research of the biopsychosocial effects of traumatic stress on soldiers and civilians. This article reviews the findings of a series of studies that examine (a) the short- and long-term mental health effects of war on combat veterans; (b) the effects of repeated exposure to war on veterans; (c) trajectories of PTSD; and, specifically, (d) reactivation and (e) delayed-onset PTSD. We present the findings of two decades of systematic trauma research, which have followed the ongoing psychopathological effect of war on veterans. In understanding the ripple effects of trauma, it can be seen that veterans do not leave the events of the war behind once they are home; rather, it is with them wherever they go. Consequently, the trauma has a ripple effect that may carry over to veterans' spouses and offspring. The multiple manifestations and trajectories of both acute and chronic trauma will be presented. Clinical ramifications and implications will also be discussed.

**Keywords: veteran, war, PTSD—posttraumatic stress disorder, trauma, stress, psychopathology**

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## INTRODUCTION

War is one of the most devastating human constructs. There are the visible results of war, such as the loss of life and the destruction of property and culture (1). However, there is also the invisible toll of psychological damage (1, 2). In the time of war, combatants not only face ongoing danger while in the active field of duty; they also witness the injury and death of their fellow soldiers, commanders, and enemies as well as innocent civilians. Moreover, combatants are not only passive bystanders, they are also perpetrators who cause death, injury, and destruction, thereby violating the ethical standards and values commonly held during peacetime (3). They struggle with loneliness, isolation, and forced separation from their loved ones alongside a lack of their physical needs being met in regard to food, drink, and sleep. Adding to the already massive stress is the unpredictability of modern warfare, including weapons of mass destruction and guerrilla warfare, which makes it difficult to predict where and when the next attack could occur (1). While most soldiers are able to adequately cope with these stressors, others become so overwhelmed by combat stress that their psychological defenses become exhausted, causing psychological breakdown.

The stress of war may have immediate, long-term, and delayed psychiatric consequences [e.g., (4–6)]. Psychological disorders resulting from war are often acknowledged either at the outbreak

or immediately following the end of the war, frequently with a lack of ongoing, systematic long-term follow-up for those who are impacted (1). Hence, much of the knowledge in this field is rather fragmented and, in many cases, knowledge that has been previously gathered does not get passed on in the event of another war (7). Moreover, the structure and diverse policies of various armies and Ministries of Defense throughout the world do not allow for systematic longitudinal studies of traumatized combatants. The unique circumstances in Israel, however, permit and even support the systematic research of traumatized veterans. Specifically, Israel has a mandatory 3-year military service for all able-bodied young adults and continuous reserve duty for men until the age of 55. Furthermore, the country is small; all Israeli wars are fought on Israeli land and its borders and, it is significant to note the close link between the Israel Defense Forces (IDF) and the Ministry of Defense. Capitalizing on these characteristics, we have initiated and conducted longitudinal studies spanning two decades of several cohorts of traumatized Israeli veterans [for details see (2, 8)].

These Israeli studies addressed many questions that had been left unanswered by previous research, as outlined by Solomon (1): What are the frequency and duration of psychiatric breakdown on the battlefield? What are the characteristic manifestations of combat-induced psychopathology? Does recurrent exposure to combat weaken soldiers or lead to greater resilience? How can we explain the many recovered combat stress reaction (CSR) casualties whose traumas are reactivated after a long asymptomatic period? Is delayed posttraumatic stress disorder (PTSD) onset a valid phenomenon? And if so what explains its onset a long time after exposure to trauma? This review article summarizes some of our studies' findings, casting light on these important questions.

## COMBAT STRESS REACTION

Combat stress reaction is the most common and conspicuous immediate psychological reaction to war, also known as shell shock, combat exhaustion, or war neurosis (2). CSR occurs when a combatant is unable to cope effectively with the threatening stimuli they are experiencing while partaking in active duty. Its diagnostic parameters include a wide range of symptoms, which may wax and wane rapidly, including restlessness, psychometric deficiencies, withdrawal from others, increased sympathetic activity, confusion, and paranoia, among others (9). The clinical picture of CSR is seen as polymorphic and labile. The most telling symptom of CSR is when the soldier is no longer able to engage in combat, thereby acting in a way that endangers the lives of his or her fellow combatants as well as him or herself (10). Unlike most psychiatric disorders, however, CSR does not allow for a clearly defined pattern of symptoms; rather, it is defined in a more general and functional way. Therefore, we considered it important to assess its typical clinical picture. We conducted a content analysis of a random sample of 104 medical charts of CSR casualties of the 1982 Lebanon War (11) and identified the following symptom clusters: psychic numbing and dissociation; anxiety symptoms, guilt about a failure to function, sense of helplessness and loneliness; and psychosomatic and psychotic-like symptoms (disorientation). Taken together, this classification of CSR is similar to that of Grinker and Spiegel (4). Although their study took place under a different cultural background and following World War II (WWII), it underscores the universality of CSR manifestations. Similar to earlier reports from World War I and WWII, the prevalence of CSR was also found to present in diverse ways during various battles and was directly related to the number of physical causalities in each battle (2).

## IS CSR SHORT LIVED AND TRANSIENT?

CSR has often been described in the international military mental health literature as a short-lived phenomenon. It has been argued that CSR is a rational reaction to an irrational situation (1) where once the distressed soldier is removed from the stressors of war, they will regain their equilibrium and functionality (10, 12). To the best of my knowledge, the majority of large-scale prospective studies of CSR have been conducted in Israel involving combatants from the 1973 Yom Kippur War [e.g., (13)] and the 1982 Lebanon War [e.g., (2, 8)]. In particular, in the Yom Kippur study, CSR casualties were identified as a high-risk group for PTSD and other psychiatric and somatic co-morbidities (13).

A more elaborated series of studies commenced during the 1982 Lebanon War as the IDF began a longitudinal research project that followed 382 CSR casualties and 334 un-afflicted control soldiers, who were carefully matched to the CSR group in sociodemographic and military characteristics [e.g., (1, 14)]. In this 20-year longitudinal study, we followed the effects of combat, namely, the resulting psychological and somatic conditions for both groups. Assessments were conducted 1, 2, 3, and 20 years after the 1982 war. Our main aim was to examine the effects of combat stress, as manifested in CSR, and to understand whether it begins and ends on the battlefield or if it continues after the war is over. We found that, for a large number of Israeli veterans, their war trauma left ongoing and disruptive sequelae. Rates of PTSD were rather high among the identified CSR combatants during the 20-year study: 1 year postwar, 54%; 2 years, 47%; 3 years, 38%; and 20 years after the war, 27%. In other words, for a substantial proportion of veterans who had a psychological breakdown on the battlefield, the war was not over when the shooting stopped. This means that for many CSR casualties, the initial breakdown on the frontline marked the beginning of a lifelong struggle with the psychopathological effects of war.

Those who experienced CSR during combat were found to have a higher likelihood to develop PTSD throughout the study. Interestingly, the long-term pathogenic effects of CSR were not only reflected in higher PTSD rates but also in its severity. Throughout the 20-year follow-up, we found that veterans who had CSR also suffered from more severe PTSD than comparable combat veterans who did not suffer from CSR (2, 8, 15). These findings speak to the predictability of CSR in later PTSD (8).

PTSD was not the only detrimental outcome found for the CSR veterans (14). The findings also revealed that these veterans endured significantly greater psychiatric symptomatology, distress, social functioning difficulties (15), health-related

problems (16), accelerated aging (17), and earlier all-cause mortality (18) than those in the non-CSR group.

Studies conducted more recently examined the effects of conflicts in Iraq, Syria, and Afghanistan. Veterans in Iraq [e.g., (19, 20)] who were assessed psychiatrically and evacuated from the frontlines received diagnoses of acute stress disorder (ASD) or acute stress reaction (ASR). Unfortunately, as these studies were after the veterans' return home it is likely that many others were overlooked who had not been evacuated and, furthermore, none used the CSR paradigm. Other systematic recent studies such as these, for example, carried out by the Danish Veterans Center, assessed PTSD symptoms rather than ASD [e.g., (21)].

The unique series of Israeli longitudinal studies of CSR casualties attests to the entrenched and enduring effects of CSR. Our findings refute the long-held notion that CSR is merely a normal yet short-lived episode that subsides once the immediate danger that combat trauma entails is lifted. Importantly, while CSR can be seen as a specific case of ASR, the two differ in that CSR is diagnosed using functional rather than symptomatic criteria (14). In other words, the psychological breakdown on the battlefield reflects the soldier's lack of restraining their fear response and returning to a stable condition (8).

CSR, as assessed in our studies, appears to be a robust marker of PTSD. Indeed, our studies indicated that, for many, CSR marks the beginning of a course of lifelong chronic PTSD and posttraumatic decline, reflected also in poor professional functioning and impaired social and familial relations (2, 15). It, therefore, transpires that CSR is not a temporary disruption, but rather a considerable and lifelong vulnerability. The experience of CSR is the quintessential moment wherein a combatant begins to feel vulnerable and helpless as they lose their senses of safety and ability (8). Another consideration is that the veterans who experienced CSR, followed by severe PTSD, may have been more at risk prior to battle than those who were not found to have CSR. At the same time, however, the CSR and comparison groups did not significantly differ in any pre-military screening, including physical and psychiatric measures (8). Although the evidence does not rule out the prior suggested possibilities, it is more plausible that CSR is the beginning of the path to the development of PTSD. Regardless of causation, based on the findings it is of the utmost importance for veterans who have experienced CSR to receive ongoing clinical support.

## EFFECTS OF REPEATED EXPOSURE TO COMBAT

The circumstances in Israel, unfortunately, have led to the necessity and ability to examine the effects of repeated exposure to combat (1). As there are few countries in the world where soldiers must continue to fight in multiple wars, there is limited knowledge on combat stress. The theoretical basis in predicting CSR derives from general psychological and somatic studies, which suggest three different perspectives. First, the vulnerability perspective [e.g., (22)] whereby exposure to stressful events on a repeated basis is a risk factor, as it depletes coping resources, increasing the individual's vulnerability. Second, the stress inoculation perspective [e.g., (23)] suggests that exposure to repeated stress is protective due to the establishment of effective coping strategies and adaptation to the situation. The third view, the stress resolution hypothesis, proposes that it is the way that a person copes with the stress that is imperative not, *per se*, the exposure to stress. Block and Zautra (24) explain further that when one is able to cope successfully with stress, they develop a sense of well-being that encourages further healthy coping, conversely, unsuccessfully coping with stress may increase one's sense of distress that further undermines their ability to cope.

To assess the effects of repeated exposure to combat, we presented the Israeli combatant participants from the 1982 Lebanon War with a list of seven Israeli wars. We then asked them to indicate which wars they were combatants in and if they had experienced CSR in those wars (2, 25). We found that the highest rates (66%) of CSR were observed among combatants who had a previous diagnosis of CSR, the lowest rates (44%) were found among those who had previously been in combat and not experienced CSR; a rate of 57% was found for those who had no previous combat experience (1). Therefore, these findings suggest that coping successfully with past stress does indeed lead soldiers to, again, cope successfully in any following combat. However, it should also be noted that soldiers with previous CSR fared worse than those without any preceding battle experience. Previous experience of CSR does not signify that a soldier will definitively experience it again if put in active duty, although, according to the results, it does leave that soldier more vulnerable the second time around. Those who do return to the battlefield are few, as they were both deemed fit to return to active military duty and expressed personal motivation to do so (1). Thus, if this highly selected group of veterans display increased vulnerability, the other CSR casualties are likely even more vulnerable.

When examining the results, it can be seen that partaking in combat over numerous wars has a deleterious effect. Among veterans with a history of CSR, the risk of subsequent CSR increases according to the number of previous wars: 57% after one war, 67% after two, and 83% after three. Among seasoned combat veterans without a history of CSR in the 1982 Lebanon War, 50% of those who fought in one previous war, 44% who fought in three wars, and 33% who fought in two wars displayed higher CSR rates (1). These findings suggest that combat scars combatants and weakens their resilience. Furthermore, despite the suggestion that previous successful coping will lead to stress inoculation, in due course repeated stress exposure will cause the fall of the strongest of soldiers.

## TRAJECTORIES OF PTSD

The course of PTSD tends to fluctuate resulting in multiple trajectories that vary in severity and duration. The literature concerning these trajectories over time include groundbreaking large-scale retrospective American epidemiological studies [e.g., (26)], later follow-ups of Vietnam veterans [e.g., (27)], systematic prospective Danish and Dutch studies [e.g., (21, 28)], and several longitudinal studies of civilians [e.g., (29, 30)]. After the inclusion of ASD in the DSM-4, there was an increasing interest, resulting

in several studies [e.g., (31, 32)]. However, the follow-up of these studies has been fairly short-term, only covering limited periods of time. Hence, the long-term course of combat induced PTSD and psychopathology requires further scientific validation.

The 20-year prospective study of Israeli veterans from the 1982 Lebanon War in relation to antecedent CSR revealed fluctuations of PTSD in both groups (8, 33). This fluctuating course was characterized by relapses/reactivations and remissions in both of the study groups. Delayed onset, defined in this study by an appearance of PTSD at any point from the measurement at the first year postwar without any previous symptoms, was reported by 23.8% of the comparison group and 16.1% of the CSR group. Specifically, 8.4% of the comparison group and 4.6% of the CSR veterans displayed PTSD only at the 20-year postwar mark, 1.2% of the comparison group and 0.8% of the CSR group at the 3-year measurement, and 3.6% of the comparison group and 2.3% of CSR group at the 2-year measurement (8).

Regarding the remissions observed in both groups (8), 7.6% of the veterans in the CSR group displayed one occurrence of remission followed by another event of PTSD, 4.6% had two remissions followed by PTSD, and 3.8% had three remissions followed by PTSD. Complete remission was seen for 3.8%; 16.8% had remission twice and 23.7% once. For the comparison group, 13.3% exhibited PTSD once, 8.4% twice, and 2.4% three times. Complete remission was seen for 3.6%; 3.6% PTSD had two remissions and, 3.6% had one remission.

## REACTIVATION OF PTSD

Of the various PTSD trajectories, two deserve special attention: reactivation and delayed onset. Reactivation is defined as PTSD that is triggered again after exposure to a subsequent stressor, often similar to the original trauma. Reactivation of stress reactions has been observed in survivors of various traumas as the current stressors reactivate anniversary reactions (34). For example, this has been found among widows who, when reminded of the loss of their spouses, experienced a reactivation of their grief [e.g., (35)]. Rape victims have also been found to have a reactivation of their trauma response upon reminders of the initial trauma (36). American WWII veterans as well as Holocaust survivors have been found to report a reactivation of wartime trauma responses coinciding with aging-related losses (37, 38). In addition, veterans from the Vietnam War have reported reactivation of their symptoms when they visited war memorials or public events that reminded them of their experience during the war [e.g., (39)].

My interest in this phenomenon began after reading the medical files of the traumatized veterans from the 1982 Lebanon War. I was struck that many veterans repeatedly spoke about their combat experiences in previous wars. To better understand this phenomena, a team of four mental health professionals carefully reviewed 35 such cases (40). We found considerable variability in relation to behavioral and functional impairment ranging from very mild to extreme.

### Uncomplicated Reactivation (23%)

These veterans appeared to have experienced a complete recovery from their previous stress reaction and did not seem to endure any further symptoms while not on the battlefield. Their current stress reactions were generally caused after an incident that triggered their prior initial traumatic experience (1).

The other participants in this study fell under the category of exacerbated PTSD. In these cases, the previous war trauma left more of an impact as the veterans continually experienced PTSD symptoms at varying degrees. For example, PTSD symptoms were found to increase while on reserve duty and also during the conscription for the 1982 Lebanon War out of anticipation of having to return to war. Additionally, these veterans were also vulnerable to experience reactivated PTSD as a result of unconnected events that did not directly threaten their immediate safety. We subdivided exacerbated PTSD into three groups (1):

### Heightened Vulnerability (51%)

These veterans experienced mild, diffused PTSD symptoms, which did not impede daily their functioning, and increased sensitivity to military stimuli. Their residual distress became fully developed PTSD after facing a direct military threat during the Lebanon War, usually not unlike the event that precipitated the original breakdown.

### Moderate Generalized Vulnerability (9%)

These veterans displayed a moderate generalized sensitivity both in their civilian lives and during reserve duty. They suffered from some residual PTSD symptoms (e.g., irritability, sleep problems, uncontrollable outbursts of anger) that somewhat impaired their functioning. When these veterans returned to the war front during the 1982 Lebanon War, they quickly developed a stress reaction in relation to rather minor military related events, with many being discharged prior to partaking in active combat.

### Severe Generalized Sensitivity (19%)

A minority of veterans suffered from PTSD symptoms throughout the time between wars. For these veterans, the arrival of their conscription order for the 1982 Lebanon War resulted in an immediate and debilitating stress reaction. Many did not even engage in combat or reach the frontline before experiencing their second psychological breakdown (41). It should be noted that all of the veterans in our study who had reactivated or exacerbated PTSD after the 1982 Lebanon War made a considerable effort to function during the 9 years between the two wars and were rather successful. Most had married and were gainfully employed, with some prospering professionally. None of the veterans had been hospitalized due to mental health issues, and all continued to participate in reserve duties despite their intensifying symptoms when faced with military stimuli. The second wave of stress reaction shed light on the psychological damage sustained during the first breakdown and further escalated it. In general, the second episode was more intense and debilitating than the first (42).

## DELAYED-ONSET PTSD

The psychological wounds of combat erupt in the form of PTSD either during or after exposure to traumatic events. The DSM-5 (43) considers delayed-onset PTSD (DPTSD) to occur when PTSD is first evident 6 months or subsequently posttrauma. Despite being acknowledged by the DSM, the validity of the existence of DPTSD has been under debate by both medical and legal professionals. This diagnosis comes into question particularly due to the possible financial benefits a veteran may receive if diagnosed with PTSD (44). Moreover, there is also the question of whether it is truly DPTSD or malingering PTSD (45). Others assert that it is the treatment or diagnosis of symptoms that is deferred rather than the actual delayed onset of the PTSD itself [e.g., (46)], meaning that PTSD may have been present and active without being properly diagnosed (47). Despite the considerable skepticism and questioning of the validity of DPTSD, many studies have supported its existence. DPTSD has been observed among survivors of various traumatic events including motor vehicle accidents (48), natural disasters (49), incest (50), and combat (51). Moreover, credible findings were reported in a meta-analysis of prospective DPTSD studies (52), providing further support for the existence of this phenomenon.

In the literature, there are inconsistent findings regarding DPTSD prevalence, process of onset, relative severity, and the relationship between acute reactions and DPTSD. For instance, estimates of DPTSD prevalence have been reported to range from 0% (23) to more than 60% (53). Therefore, we aimed to examine the prevalence of DPTSD in our prospective longitudinal study, including several follow-up measurements (44). A second remaining question relates to the timing of the appearance of DPTSD, namely, whether it occurs only after a lack of symptoms or after a culmination of ongoing symptoms (47). We, therefore, set out to study whether DPTSD symptoms occurred only after an asymptomatic period or if it surfaced after an increase in residual subclinical symptoms over time. Also left unanswered is the question of DPTSD symptom severity in relation to symptoms of PTSD that is not delayed. While some studies have failed to establish a relation between the time of PTSD onset and extent of psychopathology [e.g., (54)], others have found DPTSD to be less severe than immediate PTSD (55, 56). Therefore, assessing DPTSD symptom severity is an additional aim in our study. Furthermore, it is unclear regarding possible associations between ASD and DPTSD. To the best of my knowledge, only one study has examined this question, however, a connection was not found (56). Given the profound differences between ASD and CSR discussed above, we set out to examine the association between antecedent CSR and DPTSD.

We assessed DPTSD prevalence in Israeli veterans from the 1982 Lebanon War, both with and without antecedent CSR, with measurements at 1, 2, and 20 years after the war using two methods (44). We found that for a significant number of veterans, there were reports of DPTSD up to 20 years after the end of the war. First, when we examined all of the participants together, 16.5% were found to have DPTSD, which is higher than previously found in a majority of studies [e.g., (57)], although others have reported similar rates [e.g., (58)]. Second, in comparing only the veterans with PTSD, a higher rate of 27% endorsed DPTSD. In other previous studies, similar calculations rendered rates ranging from zero to 68% (47). Nonetheless, our finding of 27% corresponds with that of Smid et al.'s (52) meta-analysis of prospective DPTSD studies, which reported an average of 25%. Additionally, this finding gives strength to clinical observations of DPTSD that have noted endorsements of PTSD arising decades after the initial trauma and, furthermore, that delays of longer or shorter periods of time are equally likely (59).

Our comparatively high DPTSD rate also is in line with Prigerson et al. (60) and a recent short-term prospective study of Danish veterans (21) who observed that DPTSD is common in particular among war trauma survivors. There are several possible explanations for this prevalence. First, while on the battlefield, it is imperative that combatants are highly alert and functioning at their highest level. Conversely, after their return home they are able to be less aware and vigilant. In this way, soldiers will often only experience and convey feelings of distress sometime after the combat (61). A second consideration is that of the stigma related to PTSD, particularly in Israel, where there are many wars and soldiers are expected to be brave and not negatively impacted by events on the battlefield. Hence, soldiers may try to conceal, inhibit, or delay any symptoms of emotional distress (44). A third explanation, relating to the high rate of DPTSD found in our study, is that Israel could be considered a "stress lab," meaning that those who live here experience an ongoing exposure to war and terror, which, in turn, could trigger past trauma, regardless of the amount of time that has passed. DPTSD has been found to be linked to external stimuli; this implies that circumstances or events that may resemble the original trauma thereby provoke its memory [e.g., (50)]. Living under these conditions, there are many occasions where an earlier war trauma could be triggered, despite the amount of time that has elapsed.

The occurrence of DPTSD 20 years postwar found in our study is consistent with previous research that has reported prolonged delays of PTSD onset during mid-life and old age (59, 62). These stages of life come with more time to reflect and reminisce on one's life up until this point. This includes recalling past traumatic events (44) and inherent losses and endings, such as retirement, illness, and the passing of loved ones, which could be especially upsetting for trauma survivors (38), as well as reduced psychosocial resources (e.g., activities, social connections), health, and status (51, 63, 64). It also transpires that both cognitive (60) and biological (65) factors that are associated with old age are associated with DPTSD. Indeed, there is a growing understanding that DPTSD and processes related to aging could be linked (59, 66).

Possible relations between CSR and DPTSD were also explored in our study. The findings showed that experiencing a mental health breakdown on the battlefield was associated with a shorter time period until the appearance of DPTSD (44). As noted in a review of the ASD literature (14), CSR has been found to be an important predictor of ensuing and reactivated

PTSD. Our findings suggest that the presence of CSR may go beyond the prediction of PTSD and also predict when PTSD may appear.

Past studies on the intensity of DPTSD symptomology have reported varied results [e.g., (54, 55, 67)]. However, the results from our study distinctly show that with longer delays of DPTSD there was lower psychopathology. The group that was found to have DPTSD 1-year postwar was the most vulnerable, followed by the 2- and 20-year postwar onset groups, who were similar in the majority of the psychopathology measures. The no prior PTSD group had the lowest psychopathology levels, as predicted. Therefore, it could be suggested that the amount of time in the delay is a vital factor in predicting psychopathology severity. Namely, up until 1 year, there could be an increase in severity, with later delays not having as significant an impact on psychopathology.

In relation to these findings, it could be suggested that over time there is a decline in the impact of the combat and, therefore, when it is triggered after a longer period of time, it is less severe. It could also be that the PTSD was delayed as a result of more resilient coping abilities immediately following the war, which aligns with Smid et al.'s (52) findings that lower accumulative symptoms of PTSD were related to increased reports of DPTSD. Hence, it could be deduced that the aspects that played a part in the delay of PTSD for some veterans could encourage resilience for others who, thereby, do not develop PTSD. It is also possible that the resilience of these veterans is amplified by their ability to gain resources, such as supportive social networks and gainful employment during times where they are asymptomatic.

What can account for the onset of DPTSD decades postwar? This delayed onset could be due to two factors (44). First, the 20-year postwar assessment of this study took place during a particularly intense and volatile conflict between Israel and the Palestinians (Intifada Al Aqsa). During this time, Israeli civilians faced almost daily terrorist attacks, which was also found to be implicated in posttraumatic distress (68) and, hence, these events could justifiably trigger DPTSD. Second, in regard to the 20-year delayed PTSD, the delay could be due to the stage of life of the veterans who were entering into their mid-life, with its abovementioned losses and reflections.

In general, it was found that veterans with CSR experienced a higher severity of DPTSD than those without CSR (44). This corresponds to previous studies that have reported individuals with ASD (69) and CSR (15) to be at a higher risk for subsequent psychopathology. It is also in line with the "vulnerability perspective," which suggests that experiencing a primary trauma may compromise effective coping strategies in later events of distress (70). Additionally, stress sensitization, whereby exposure to severe stress could increase responsiveness during future stressful events, has been proposed as a possible underlying mechanism in DPTSD in several studies (71, 72) and has also received empirical support (73), meaning that CSR could contribute to this sensitivity.

## DOES DPTSD ERUPT AFTER A TRULY ASYMPTOMATIC PERIOD?

We found that, in general, DPTSD occurred following residual PTSD symptoms. Specifically, among the 2-year postwar and 20-year postwar DPTSD onsets as well as the no prior PTSD group there was evidence of an increase in existing symptoms before the onset of PTSD (44). This is supported by Smid et al.'s (52) findings that DPTSD frequently results from an increase in subthreshold PTSD symptoms as well as research regarding DPTSD in non-combat related traumas (47, 59, 74). One explanation that has been recently suggested as a model for DPTSD is "fear incubation" (75), whereby fear conditioning results in increasing fear and anxiety over time. Studies of rats have reported that, post-fear training, conditioned fear responses were markedly higher after 31 and 61 days than after 2 or 15 days (76). As such, fear incubation replicated a heightened response to trauma triggers over time, similar to that seen in DPTSD. In another animal PTSD study (77), after classical conditioning, an amplified response was found after a similar period of delay. This type of response is known as "conditioning-specific reflex modification" (CRM) and has been found to be relevant for specific aspects of PTSD (78). Their results showed a pattern similar to that of PTSD symptoms that have a delayed presentation as, when they appear, they continue and worsen over time. In our study, DPTSD emerged among a small number of participants after an asymptomatic period. Although some are of the opinion that this is an unlikely manifestation of PTSD [e.g., (79)], this pattern of DPTSD has been previously reported by others [e.g., (80)], particularly in case studies (81).

## LIMITATIONS

This series of studies has several methodological limitations to consider. First, self-report measures were used that, although often found in trauma studies, may have a risk of biased reporting. Another limitation is related to the timing of the measurements. Due to the gap between the assessments, there is a lack of data regarding the veterans' potential PTSD between the waves of measurement. Furthermore, attrition may have had an impact in this longitudinal study. Although sophisticated missing data strategies were employed, it must be acknowledged that participant drop-off may have unknowingly affected our results. The study was conducted among Israeli combat veterans who fought in the same war and thus share a similar social and cultural characteristic. Generalization from these results to other populations, in other times and cultures, should be undertaken cautiously. Finally, this review is not systematic and there is no meta-analytic data and so the validity of the findings is somewhat limited.

Despite these limitations, the present series of studies make important contributions to the literature on veterans' mental health. The studies are based on a prospective design that commenced on the battlefield and continued over a 20-year follow-up period. Following veterans over such an expanse of

time allows for a unique opportunity in the study of prevalence, correlations, and the clinical picture of combat-induced PTSD.

## CLINICAL IMPLICATIONS

These studies entail important theoretical implications. First, our results propose that the deleterious effects of combat are deep and enduring. The findings also highlight the significance of CSR in predicting subsequent PTSD and debilitating comorbidities. The transition from CSR to PTSD is an evolving process. It is seen as a window of opportunity for prevention of PTSD. Previously, this disorder crystallized and became entrenched and debilitating. In fact, we capitalized on our longitudinal studies of the CSR casualties of the 1982 Lebanon War and assessed the effectiveness of Front Line treatment and found that 1 year and 20 years after the war, CSR casualties who were treated using this modality suffered from much lower rates of PTSD and led more productive and stress-free lives (82, 83). Interventions for the acute phase should be adopted to impede and halt the progression from the acute to the chronic phase.

The longitudinal design indicates that the course of PTSD has considerable variability, with numerous trajectories, varying in duration and severity. Our findings also confirm the actuality of PTSD reactivation and DPTSD. The rates reported in this study unquestionably demonstrate that DPTSD is not a trivial or non-existent phenomenon. Therefore, it should be acknowledged as being one form that PTSD can take while having a unique clinical profile. Finally, the results also indicate that the presence of CSR is a significant risk factor, not only for PTSD but also for those who develop PTSD after a shorter delay.

There are also important practical implications to consider. PTSD is the only known disorder to specifically result from exposure to a traumatic event, which often involves medical, legal, and political implications. Traumatized veterans who are sent to war by their home countries must have and deserve long-term support, monitoring, and professional attention, specifically due to the labile nature of the PTSD course and particularly concerning reactivated PTSD and DPTSD.

With regard to DPTSD, mental health professionals are encouraged to closely follow their patients' emerging symptoms, whether or not the clinical threshold for PTSD has been reached. Also, the knowledge that psychopathology varies among those with PTSD could be imperative for therapists. Moreover, the timing of the PTSD onset must also be established, as it could have an effect on decisions regarding treatment. Additionally, as PTSD consists of unique subtypes, therapists should be encouraged to design interventions specifically for veterans with PTSD related conditions [e.g., (84)]. Finally, and most importantly, the plight of traumatized veterans across the globe stems from man's proclivity for aggression and the tendency of nations to settle political conflicts *via* wars. The lifelong suffering of traumatized veterans and their families, *via* secondary traumatization should be acknowledged and treated.

## AUTHOR CONTRIBUTIONS

ZS made all of the contributions to the work and approved it for publication.

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# Self-Disgust Is Associated With Loneliness, Mental Health Difficulties, and Eye-Gaze Avoidance in War Veterans With PTSD

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In the present study, we examined, for the first time, the association between self-disgust, loneliness, and mental health difficulties in war veterans diagnosed with PTSD. For this purpose, we used a mixed methods design, incorporating surveys and a novel eye-tracking paradigm, and compared the findings from the PTSD veteran group ($n$ = 19) to those from a general population group ($n$ = 22). Our results showed that the PTSD veteran group reported almost three times higher scores in self-disgust, and significantly higher scores in loneliness and mental health difficulties (anxiety and depression), compared to the general population. Furthermore, self-disgust mediated the association between loneliness and anxiety symptoms in both groups. The results from the eye-tracking paradigm further showed that veterans with PTSD displayed a self-avoidance gaze pattern, by looking significantly more toward pictures of faces of unknown others and away from their own face—a pattern that was not replicated in the general population group. Higher self-disgust scores were significantly associated with longer total gaze to the pictures of others (vs. the self). Our findings have implications for the role of self-disgust in the mental health of war veterans.

**Keywords: loneliness, self-disgust, war veterans, PTSD, depression, anxiety**

## INTRODUCTION

Posttraumatic stress disorder (PTSD) can be conceptualized as a cluster of symptoms resulting from extremely traumatic life-threatening experiences, for example, war experiences (Sher, 2005). Diagnosing PTSD requires symptoms to have developed after the traumatic experience and the prevalence of PTSD among war veterans in the United Kingdom ranges between 4% and 12%, and varies from 2% to17% worldwide (e.g., Hotopf et al., 2006; Lee et al.). If the war stressor is chronic

and especially if cruelty is involved (i.e., when war captivity and/or maltreatment are involved), the prevalence of PTSD among survivor veterans can be as high as 80–90% (Kramer et al., 1994; Tanielian et al., 2008).

Loneliness (i.e., the subjective feeling of lack of meaningful social relationships) is prevalent among war veterans (Kuwert et al., 2014; Solomon et al., 2015). Research has indicated that 44% of war veterans experience feelings of loneliness at least some of the time, and 10.4% reported often feeling lonely (Kuwert et al., 2014). Solomon and Dekel (2008) found that increased levels of PTSD among war veterans were positively associated with higher levels of self-reported loneliness. More recent studies in Israeli veterans have also shown that loneliness was cross-sectionally and longitudinally associated with posttraumatic stress reaction (Solomon et al., 2015) and posttraumatic growth (Stein et al., 2018). Combat stress seems to contribute to the development and maintenance of loneliness across time (Solomon et al., 2015) for two reasons; firstly, on the battlefield, soldiers that are exposed to trauma feel alone and defenseless, and secondly, during the homecoming period war veterans feel estranged and isolated from society because they feel that others cannot understand them (Solomon et al., 2015). As a result, they tend to report higher levels of social avoidance (Galovski and Lyons, 2004) and psychosocial difficulties (Pietrzak et al., 2010), less social support, poorer social functioning and lower life satisfaction (Tsai et al., 2012) compared to non-PTSD veterans.

Posttraumatic stress disorder is also highly comorbid with depression (Blanchard et al., 1998), anxiety (Spinhoven et al., 2014), suicidality (Kramer et al., 1994; Oquendo et al., 2003, 2005; Sher, 2005) and bipolar disorder (Dilsaver et al., 2007). In war veterans, the triple comorbidity of PTSD with anxiety and depression ranges between 11–67% (Brady and Clary, 2003; Hashemian et al., 2006; Ginzburg et al., 2010). Although there are arguments suggesting that this triple comorbidity may be the result of measurement artifacts and symptoms overlap (e.g., Franklin and Zimmerman, 2001) or shared risk factors (e.g., Hoven et al., 2005; Schumm et al., 2006; Vinck et al., 2007), longitudinal data suggests otherwise. Specifically, it has been shown that PTSD symptoms are more stable across time, and that symptoms of depression and anxiety are developed later than PTSD (Ginzburg et al., 2010).

## Self-Disgust and PTSD

Self-disgust is a negative self-conscious emotional schema that originates from the basic emotion of disgust and is directed toward physical (physical self-disgust; e.g., "I find myself repulsive") or behavioral aspects of the self (behavioral self-disgust; e.g., "I often do things I find revolting"; Overton et al., 2008). Over the last decade, research has shown that self-disgust has been associated with a range of psychological difficulties, including social anxiety (Amir et al., 2010 insomnia (Ypsilanti et al., 2018), impaired body image and disordered eating behavior (Espeset et al., 2012; Olatunji et al., 2015), and PTSD symptoms in women with a history of sexual assault (for a recent review see Clarke et al., 2019). The role of self-disgust in such traumatic experiences in females has been related to mental contamination (Badour et al., 2013), a state that is experienced predominately in relation to moral rather than physical violations. In this case, the victims report feeling "dirty inside" and demonstrate higher self-directed disgust (Coughtrey et al., 2012).

Several studies have also highlighted the mediating properties of self-disgust on the association of cognitive processes and socio-emotional experiences with mental health outcomes. In particular, self-disgust has been found to mediate the association between dysfunctional thoughts and depression (Powell et al., 2013); loneliness and depressive symptoms in the general population (Ypsilanti et al., 2019); loneliness and anxiety symptoms in older adults (Ypsilanti et al., 2020); and PTSD symptoms (PCL-5 sub-clusters of avoidance, re-experiencing, changes in cognition and affect) and suicide risk (Brake et al., 2017) in undergraduate students. More specifically, self-disgust significantly mediated the relationship between all the sub-clusters of PCL-5 outlined in the DSM-IV-TR (American Psychiatric Association [APA], 2000) and suicide attempts. However, thus far no study has examined self-disgust in war veterans diagnosed with PTSD and its role in the development of loneliness and mental health outcomes.

## Eye-Tracking, Attentional Avoidance, and Self-Disgust

In anxiety disorders, one of the most common ways to measure attentional vigilance and disengagement to threatening stimuli is to use reaction time (RT) tasks (see Armstrong and Olatunji, 2012 for a meta-analysis). In these tasks, participants are briefly exposed to threatening stimuli (e.g., 500ms), and are asked to respond to these by pressing a button (e.g., Bar-Haim et al., 2007). According to the vigilance hypothesis, individuals with anxiety disorders show hypersensitivity to threat and, therefore, respond faster to threatening stimuli compared to non-anxious individuals (Wiens et al., 2008). Alternately, the maintenance hypothesis suggests that participants exhibit difficulty disengaging from threatening stimuli such as sad pictures, which takes place after threat detection and is commonly observed in individuals with depression (Fox et al., 2001). However, RT tasks are less able to detect attentional avoidance in affective disorders, which may come into play at later stages of stimulus exposure (Cisler and Koster, 2010). Attentional avoidance is more voluntary and strategic and less automatic; therefore, it requires continuous and prolonged tasks of visual attention. (Armstrong and Olatunji, 2012). Eye-tacking methodology provides a unique opportunity to study vigilance and avoidance in affective disorders as it allows individuals to naturally dwell on the dysphoric stimuli for longer exposure times. In this context, vigilance is conceptualized as initial orientation of eye gaze to the stimulus (time to first fixation within the first second of exposure) and avoidance comes later because it requires a more conscious, voluntary evaluation of the dysphoric stimulus (Mogg et al., 1987). In other words, the individual strategically "*decides*" to avoid directing attention to the threatening stimulus.

Qualitative studies have shown that people who experience high self-disgust report that they avoid looking at their own

reflections on the mirror: "I'll suddenly, um, feel quite disgusted, possibly by my appearance, or you know, when I look in the mirror or happen to see myself in a reflective surface" and "I've got a lot of friends that, you know, like every time they go past. . .a shop window or something, they're like. . .whereas. . .I'll do anything to like avert my gaze" (Powell et al., 2014, p.568). An eye-tracking paradigm could allow for the assessment of attentional avoidance mechanisms in self-disgust. Moreover, people with higher levels of self-disgust may display increased attentional vigilance to others because they tend to perceive themselves as social "contaminants": "What am I doing with all these people and just making them feel like there's something horrible in the room. I should just go home and out of the way and stop making them look at me" (Powell et al., 2014, p. 571). In support of this argument, a recent eye-tracking study (Ypsilanti et al., 2020) found that older adults with higher levels of self-disgust displayed attentional avoidance to images of their own face, compared to the faces of unknown others. Based on this evidence, it is plausible that individuals with PTSD may display different responses to the faces of other people compared to when looking at their own image particularly in later stages of stimulus exposure.

## The Present Study

Previous research has examined the association between self-disgust and PTSD symptoms among females who had experienced sexual assault (Badour et al., 2012, 2013, 2014), but no study, so far, has examined the association of self-disgust with mental health difficulties among war veterans suffering from PTSD. Given that self-disgust is present in PTSD and trauma-related conditions that are not specifically pertinent to sexual assault (see Clarke et al., 2019) and that war veterans tend to experience greater mental health difficulties than the general population (Pietrzak et al., 2010; Tsai et al., 2012), it is theoretically plausible that self-disgust will be higher among war veterans with PTSD than in non-veterans and individuals without PTSD.

Furthermore, previous research has suggested that self-disgust mediated the association of loneliness with both depression and anxiety symptoms in the general population (Ypsilanti et al., 2019, 2020). It is possible that this effect can be extended to the study of PTSD among war veterans for the following reasons. Firstly, loneliness is highly prevalent among war veterans (Solomon and Dekel, 2008), and PTSD is highly comorbid with depression (Brady and Clary, 2003; Hashemian et al., 2006; Ginzburg et al., 2010), but the process that links loneliness and depression in this population remains unclear. Secondly, if loneliness contributes to the development of depressive and anxiety symptoms through self-disgust (Ypsilanti, 2018; Ypsilanti et al., 2019, 2020), then it is plausible that self-disgust may potentially explain the association of loneliness with anxiety and depression symptoms in war veterans with PTSD.

On the basis of these arguments, in the present study we hypothesize that war veterans with PTSD will exhibit higher levels of loneliness, self-disgust, and symptoms of depression and anxiety compared to a sample of the general population without PTSD history (Hypothesis 1).We also hypothesized that self-disgust would mediate the relationship between loneliness and symptoms of anxiety and depression in veterans with PTSD (Hypothesis 2). In order to further explore the role of self-disgust in mental health outcomes in war veterans with PTSD we will use a novel task to measure attentional vigilance and maintenance with an eye-tracking paradigm. Based on the "avoidance hypothesis" suggested by Powell et al. (2014) we anticipate that participants with PTSD will avoid looking at pictures of their own face compared to pictures of faces of unknown others (Hypothesis 3; Ypsilanti et al., 2020). Finally, we hypothesize that there will be a correlation between self-disgust scores and the relative difference of total eye gaze duration for self over eye gaze duration for others (Hypothesis 4).

# MATERIALS AND METHODS

## Participants

Forty-two participants were recruited. Nineteen PTSD-diagnosed male veterans from the HM Armed Forces, aged between 24 and 64 years ($M$ = 47.84, $SD$ = 9.09) and 22 participants without PTSD history were selected from the general population, aged between 20 and 66 years ($M$ = 45.40, $SD$ = 13.17, males = 43.5%)—henceforth, referred to as non-PTSD participants. Power analysis was conducted with G*Power (v.3.0.10) to determine the sample size required to detect significant effects in the eye-tracking task and the regression analyses ($p < 0.05$). For the eye-tracking paradigm, we used the effect sizes reported in related published research on eye gaze in high and low self-disgust groups (i.e., Ypsilanti et al., 2020). Based on those parameters (Cohen's $f$ = 0.32, $\alpha$ = 0.05, power = 0.95), it was determined that a total sample of 24 participants would sufficiently detect significant effects. Accordingly, using the data from related published research (i.e., Ypsilanti et al., 2019, 2020) we calculated that in order to detect a large multivariate effect size ($f^2$ = 0.58, $\alpha$ = 0.05, power = 0.95, with two predictor variables) in the multiple regression analysis, we needed a total sample of 25 participants.

All PTSD diagnosed veterans reported having a diagnosis of the condition preceding data collection by at least 12 months, with their respective diagnoses directly relating to varied theaters of conflict around the world; dating back to 1982 (The Falklands) and as recent as a few years ago (Afghanistan). The PTSD-diagnosed participants were recruited via networks that were established alongside various veteran PTSD support groups and care agencies. The research was carried out in accordance with the Code of Human Research Ethics of the British Psychological Society, and participants were provided with consent forms to complete, and were duly informed about their participation rights (i.e., voluntary and anonymous participation; no penalties for withdrawing from the study at any stage without notice).

## Measures

### Demographics

Demographic characteristics were assessed with open-ended questions asking participants to indicate their age

(i.e., How old are you?), gender, and nationality. War veterans were also asked to about their military background and service.

### Posttraumatic Stress Disorder Measure

The PTSD Checklist for DSM-5 (PCL-5, Blevins et al., 2015) is a 20-question assessment tool of a person's PTSD symptomatology, addressing each of the required Criteria B, C, D, and E from DSM-5 (American Psychiatric Association [APA], 2013). Questions are Likert scaled, ranging from zero (not at all) to four (extremely), such as (in the past month how much were you bothered by) "repeated, disturbing dreams of the stressful experience," "trouble remembering important parts of the stressful experience," and "feeling jumpy or easily startled." Scores range from 0 to 80, a higher score indicative of a higher level of PTSD symptomatology, with a stipulated score of 33 suggested as a threshold for consideration of further assessment toward a potential PTSD diagnosis. In the present study, the PCL-5 had high internal consistency reliability (Cronbach's $\alpha = 0.95$).

### Loneliness

The University of California Loneliness Scale (UCLA-3) was used in the present study (Russell, 1996) as a measure of loneliness, which consists of 20 items (e.g., "I am unhappy doing so many things alone," "I feel completely alone," and "I feel isolated from others") rated on a 4-point scale of (1 = *never*, 4 = *often*). Loneliness scores are calculated by summing the items (after reverse scoring) and ranged from 20 to 80, with higher scores indicating increased loneliness levels. Cronbach's alpha was high ($\alpha = 0.89$).

### Depression

Depressive symptomatology was measured using the Beck's Depression Inventory (Beck et al., 1961), which measures characteristic attitudes and symptoms of depression and consists of 21 self-report items (e.g., "I feel sad," "I feel discouraged about the future," "I feel guilty all the time," and "I am disgusted with myself") rated on a 4-point scale (0–3, with variable anchors) giving a total score maximum of 63. Internal consistency reliability for the BDI in the present study Cronbach's alpha was high ($\alpha = 0.91$).

### Self-Disgust

Self-disgust was assessed with the Self-Disgust Scale (SDS; Overton et al., 2008), an 18-item measure reflecting disgust and repulsion directed to the self. Six items are filler items (e.g., "I enjoy the company of others") and 12 items reflect self-disgust toward the self (e.g., "I find myself repulsive"), and toward one's behavior/actions (e.g., "I often do things I find revolting"). Responses are coded on a 7-point Likert scale (1 = *strongly agree*, 7 = *strongly disagree*), and, after reverse scoring 9 items, a total sum score is computed. Higher scores indicate higher levels of self-disgust. In the present study, the internal consistency reliability coefficient for the self-disgust scale was high (Cronbach's $\alpha = 0.91$).

### Anxiety

The State/Trait Anxiety Inventory (STAI) (Spielberger, 1983) was used to measure trait anxiety in all participants. There are 10 Likert scale questions, graded from one (Not at all) to four (Very much so); such as "I feel tense," "I feel nervous," and "I feel steady." Larger scores indicated a higher level of anxiety, and the internal consistency reliability coefficient in the present study was high (Cronbach's $\alpha = 0.95$).

## Eye-Tracking Task/Apparatus

A Tobii TX300 mobile eye tracker was used to record eye gaze for images of the self and other unknown faces. The Tobii TX300 provides high-quality fixation data through a non-invasive measure, allowing slight movements and comfort of the participants (Tobii, 2016). The stimulus created on Tobii Studio Software used 12 facial photographs (6 female, 6 male) showing neutral expressions from the Karolinska Directed Emotional Faces Database (Lundqvist et al., 1998). All photographs were cropped into an oval shape, removing hair, neckline and any other background stimulus that could also distract attention. Each oval-shaped face had the approximate dimensions of 401 × 578 mm. The presentation encompassed 48 slides, each presenting 2 faces alongside each other on a white background (**Figure 5**). Each slide was presented for 5 s and every slide separated with a control slide presenting a single fixation cross in the center of the screen. Half of these slides (24) included the participants' own photograph as one of the faces displayed, also cropped in the same oval shape. The rest of the slides depicted two unknown faces. All slides were counterbalanced to ensure there was no preference shown to a particular side of the screen (left/right). Participants either saw slides presenting two unknown faces or one unknown face and their own face.

## Design/Procedure

A cross-sectional, correlational design was used to measure the associations between demographic characteristics (age, gender, and nationality), self-disgust, depressive symptomatology, loneliness, and anxiety in the two groups. No time restrictions were applied and survey completion required approximately 15–20 min. A mixed factorial design was used to investigate attentional vigilance (measured by time to first fixation in second 1) and attentional avoidance (measured by total visit duration across time blocks). The repeated measures factors were type of image (self vs. other) and time (2, 3, 4, 5 s). The between subjects factor was group (PTSD vs. non-PTSD).

Upon arrival participants were asked whether they were willing to have their photo taken for the purposes of the study and signed consent for participating in the study and having their photo taken. This information was not provided before arrival so as to avoid beautification preparations for the photograph. A single picture was taken of the face of each participant using a digital camera that was then cropped in an oval shape and sized as described in the apparatus section above. All pictures were taken from the same distance and in a neutral background. Participants were then asked to complete the demographic questionnaire and loneliness scale while the researcher cropped and uploaded their own photo in the Tobii eye-tracker (approximately 10 min). All participants completed the remaining questionnaires after the end of the

eye-tracking study. Photographs were deleted from the digital camera (permanent deletion) in front of the participant at the end of the study, and participants were fully debriefed about the purposes of the study. They were also given the right to withdraw their data from the study up to 7 days after the data collection by giving them a unique identification code. Ethics approval for the study was granted by the respective Ethics Review Board of the host institution.

## Data Analysis

Multivariate analysis of variance was used to compare differences in self-disgust scores, loneliness, depression and anxiety between individuals with PTSD and non-PTSD participants. Hierarchical linear regression analysis models were used to test the hypothesized relationships between the constructs. Regression-based multiple mediation analysis with bootstrapping (Preacher and Hayes, 2008; Hayes and Preacher, 2014) was further used to assess the indirect association between loneliness, anxiety and depressive symptoms in the two groups, via self-disgust. Finally, repeated measures ANOVAs were used to examine differences in time to first fixation and total gaze duration in the two groups. All data were analyzed in SPSS v. 22 (IBM Corp, 2013) and Jamovi Version 0.9 (The Jamovi Project, 2019)[1].

# RESULTS

## Group Differences in Loneliness, Self-disgust, Anxiety, and Depression

To examine the first hypothesis, that PTSD veterans will exhibit higher levels of loneliness, self-disgust, and symptoms of depression and anxiety compared to non-PTSD participants, we performed a one-way between groups MANOVA with four dependent variables. Our results indicated a significant main effect of group on self-disgust, $F(1,41) = 50.49$, $p = 0.000$, $\eta_p^2 = 0.564$; loneliness, $F(1,41) = 48.27$, $p = 0.000$, $\eta_p^2 = 0.553$; depression $F(1,41) = 112.18$, $p = 0.000$, $\eta_p^2 = 0.742$; and anxiety, $F(1,41) = 41.16$, $p = 0.000$, $\eta_p^2 = 0.514$. In all variables war veterans with PTSD scored significantly higher than the comparison group with large effect sizes (Cohen, 1992) and substantially raised scores in the self-disgust scale. Descriptive statistics are presented in **Table 1**.

**TABLE 1 |** Between group differences in self-disgust, loneliness, depression, and anxiety.

| | PTSD veterans (*N* = 19) | | Non-PTSD healthy controls (*N* = 22) | |
|---|---|---|---|---|
| | *M* | *SD* | *M* | *SD* |
| Self-disgust | 55.36 | 12.66 | 28.27 | 11.73 |
| Loneliness | 58.68 | 8.44 | 36.09 | 11.79 |
| Depression | 32.00 | 9.62 | 5.72 | 6.08 |
| Trait anxiety | 30.10 | 5.51 | 18.04 | 6.38 |

## Direct Effects of Loneliness and Self-Disgust on Depression and Anxiety Symptoms

Four hierarchical linear regression models were used to assess the associations between loneliness and self-disgust with depression and anxiety symptoms in PTSD and non-PTSD participants respectively (Hypothesis 2). The models in each group were completed in two steps with the first step including loneliness, and the second step included self-disgust. Entering the predictor variables in this sequence allows us to examine the unique effects of self-disgust on anxiety and depression after taking into account the effect of loneliness. Additionally, having separate analyses for PTSD and non-PTSD participants allows us to examine if the patterns of associations observed between loneliness, self-disgust and anxiety and depression symptoms separately in the two groups. In all four models, tolerance levels between the predictor variables were high (>0.523), suggesting no multicollinearity. Additionally, the observed multivariate effect sizes ($f^2$) were determined based on Cohen (1992) conventions, and ranged from 1.68 to 3.54, indicating large effects.

In the PTSD group, the results showed that a significant model ($F = 16.16$, $p = 0.001$) emerged predicting 62.8% (Adjusted $R^2$) in depression symptoms. At the first step of the analysis, loneliness was significantly associated with depression symptoms ($\beta = 0.818$, $p < 0.001$), and this effect was also retained after adding self-disgust in the second step. Self-disgust was not significantly associated with depression symptoms in the PTSD group.

The second model in the PTSD group was also statistically significant ($F = 16.60$, $p < 0.001$) and predicted 63.4% (Adjusted $R^2$) in anxiety symptoms. At the first step of the analysis, loneliness was significantly associated with anxiety symptoms ($\beta = 0.758$, $p < 0.001$). However, the effect of loneliness was reduced ($\beta = 0.476$, $p = 0.02$) after adding self-disgust, which was significantly associated with anxiety symptoms ($\beta = 0.424$, $p = 0.04$). Adding self-disgust in the final step of the analysis significantly increased predicted variance in anxiety symptoms ($\Delta R^2 = 10\%$, $F_{\text{change}} = 4.94$, $p = 0.04$). The results from both regression models for the PTSD group are summarized in **Table 2**.

In the non-PTSD participants, the analysis showed that a significant model emerged ($F = 32.20$, $p < 0.001$) predicting 74.8% (Adjusted $R^2$) of the variance in depression symptoms. At the first step of the analysis, loneliness was significantly associated with depression symptoms ($\beta = 0.822$, $p < 0.001$). At the second step, self-disgust was entered and significantly increased predicted variance in depression symptoms ($\Delta R^2 = 9.6\%$, $F_{\text{change}} = 8.02$, $p = 0.01$), was associated ($\beta = 0.429$, $p = 0.01$) with the criterion variable, and reduced the effect of loneliness ($\beta = 0.526$, $p = 0.003$).

The second model in the non-PTSD participants was also significant ($F = 38.30$, $p < 0.001$) and predicted 78% (Adjusted $R^2$) of the variance in symptoms of anxiety. At the first step of the analysis, loneliness was significantly associated with anxiety symptoms ($\beta = 0.821$, $p < 0.001$). At the second step, self-disgust

[1]Retrieved from https://www.jamovi.org

was entered in the analysis and significantly increased predicted variance in anxiety symptoms ($\Delta R^2$ = 12.7%, $F_{change}$ = 12.14, $p$ = 0.002), was associated (β = 0.493, $p$ = 0.002) with the criterion variable, and reduced the effect of loneliness (β = 0.481, $p$ = 0.003). The results from both regression models for the non-PTSD participants are presented in **Table 3**.

## Indirect Effects of Loneliness on Depression and Anxiety Symptoms

Using the Preacher and Hayes (2008) approach, three mediation models were used to assess the indirect associations, via self-disgust, of loneliness with depression and anxiety symptoms in the PTSD and non-PTSD participants. Specifically, the first mediation model examined the indirect effect of loneliness on anxiety symptoms in the PTSD group, and showed that self-disgust had a significant mediation effect ($z$ = 1.99, $p$ = 0.04; **Figure 1**). The second and third models examined the indirect effects of loneliness, via self-disgust, on depression and anxiety symptoms respectively in the non-PTSD participants. The results showed that self-disgust mediated the association of loneliness with both depression ($z$ = 2.46, $p$ = 0.01 **Figure 2**) and anxiety symptoms ($z$ = 2.80, $p$ = 0.005 **Figure 3**).

## Eye-Tracking Data

Eye-tracking data were analyzed after determining the areas of interest (AoI) in Tobii studio. AoI were the persons' own face in slides that depicted the "self" alongside a face of an unknown other. Then we defined AoI the "other" face in slides that depicted the "self" alongside a face of an unknown other. We extracted two metrics for these AoI, time to first fixation (TFF) and total visit duration (TVD). In the final analysis we compared TFF and TVD toward the "self" picture and the "other" picture in both groups. A 2 × 2 repeated measures ANOVA was used to assess attentional vigilance from differences in time to first fixation toward their own picture and the picture of an unknown other between the two groups (PTSD vs. non-PTSD) for each Type of Stimulus (self vs. other). There was no significant main effect of group, $F(1,39)$ = 0.98, $p > 0.05$, or Type of Stimulus, $F(1,39)$ = 2.66, $p > 0.05$, and there was no significant interaction, $F(1,39)$ = 0.47, $p > 0.05$. This means that there were no differences in attentional vigilance between the two groups when looking at their own face and the faces of unknown others. To examine attentional avoidance we used a 2 × 2 × 4 repeated measures ANOVA with group (PTSD, non-PTSD) as a between subject factor and Type of Stimulus (picture of self vs. picture of unknown other) and time blocks (2 seconds, 3 seconds, 4 seconds and 5 seconds) as repeated measures factors and compared total eye gaze duration in each second. There was a significant main effect of Time Blocks, $F(3,39)$ = 5.56, $p$ = 0.001, $\eta_p^2$ = 0.12, and a significant interaction between Type of Stimulus × Group, $F(1,39)$ = 4.91, $p$ = 0.03, $\eta_p^2$ = 0.11. Means and SDs of each group across 4 time blocks are presented in **Table 4**.

We further explored the avoidance hypothesis using 2 × 4 repeated measures ANOVAs for each group separately. For the non-PTSD participants there was a significant main effect of Time Block, $F(3,21)$ = 3.87, $p$ = 0.013, $\eta_p^2$ = 0.15, and a significant interaction Type of Stimulus and Time Block, $F(3,63)$ = 2.96, $p$ = 0.039, $\eta_p^2$ = 0.12 (**Figure 4**). Planned *post hoc* comparisons indicated a significant increase in total eye gaze toward their own face from second 2 to second 3, $t$ = 4.61, $p < 0.001$, df = 21, and second 4, $t$ = 3.25, $p$ = 0.004, df = 21. No other differences were significant. For the PTSD group there was a significant main

**TABLE 2 |** Associations between loneliness, self-disgust, depression and anxiety in the PTSD group.

| | Depression symptoms | | | | Anxiety symptoms | | | |
|---|---|---|---|---|---|---|---|---|
| | ***B*** | β | **95% CI for B** | **Adjusted $R^2$** | ***B*** | β | **95% CI for B** | **Adjusted $R^2$** |
| Step 1 | | | | 0.649 | | | | 0.549 |
| Loneliness | 0.932 | 0.818** | 0.597, 1.268 | | 0.495 | 0.758** | 0.277,0.713 | |
| Step 2 | | | | 0.628 | | | | 0.634 |
| Loneliness | 0.929 | 0.815** | 0.464, 1.394 | | 0.311 | 0.476* | 0.047,0.575 | |
| Self-disgust | 0.003 | 0.005 | -0.307,0.313 | | 0.185 | 0.424* | 0.009,0.361 | |

*Note: *p ≤ 0.05; **p ≤ 0.001.*

**TABLE 3 |** Associations between loneliness, self-disgust, depression and anxiety in the non-PTSD group.

| | Depression symptoms | | | | Anxiety symptoms | | | |
|---|---|---|---|---|---|---|---|---|
| | ***B*** | β | **95% CI for B** | **Adjusted $R^2$** | ***B*** | β | **95% CI for B** | **Adjusted $R^2$** |
| Step 1 | | | | 0.660 | | | | 0.658 |
| Loneliness | 0.425 | 0.822*** | 0.287,0.562 | | 0.445 | 0.821*** | 0.301,0.589 | |
| Step 2 | | | | 0.748 | | | | 0.780 |
| Loneliness | 0.272 | 0.526** | 0.108,0.435 | | 0.260 | 0.481*** | 0.100,0.421 | |
| Self-disgust | 0.222 | 0.429* | 0.058,0.387 | | 0.268 | 0.493* | 0.107,0.429 | |

*Note: *p ≤ 0.05; **p ≤ 0.005; ***p ≤ 0.001.*

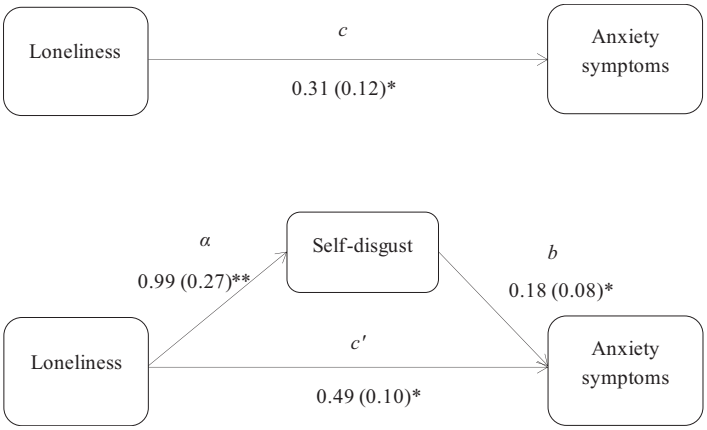


**FIGURE 1 |** Self-disgust mediates the association between loneliness and anxiety symptoms in the PTSD group. *Note*: The total (c) and the indirect effect (c') of loneliness on anxiety symptoms are shown; Unstandardized path coefficients are presented, with standard errors in brackets. *$p \leq 0.05$; **$p \leq 0.005$.

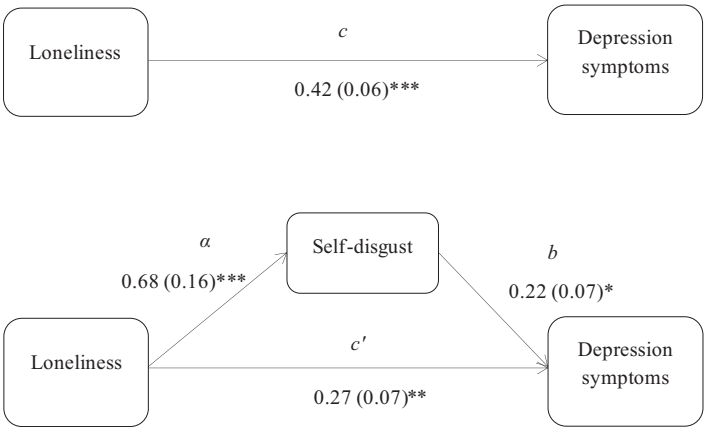


**FIGURE 2 |** Self-disgust mediates the association between loneliness and depression symptoms in the non-PTSD group. *Note*: The total (c) and the indirect effect (c') of loneliness on depression symptoms are shown. Unstandardized path coefficients are presented, with standard errors in brackets. *$p \leq 0.05$; **$p \leq 0.005$; ***$p \leq 0.001$.

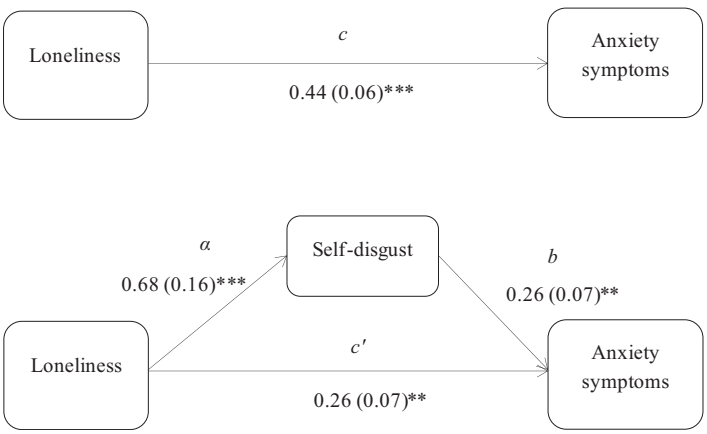


**FIGURE 3 |** Self-disgust mediates the association between loneliness and anxiety symptoms in the non-PTSD group. *Note*: The total (c) and the indirect effect (c') of loneliness on anxiety symptoms are shown. Unstandardized path coefficients are presented, with standard errors in brackets. *$p \leq 0.05$; **$p \leq 0.005$; ***$p \leq 0.001$.

**TABLE 4 |** Means and SDs of total eye gaze (measured by total visit duration) to the picture of the self and the picture of an unknown other in PTSD and non-PTSD groups across time blocks.

| | PTSD veterans (*N* = 19) | | Non-PTSD healthy controls (*N* = 22) | |
|---|---|---|---|---|
| | *M* | *SD* | *M* | *SD* |
| Total visit duration to self (second 2) | 0.50 | 0.16 | 0.55 | 0.15 |
| Total visit duration to self (second 3) | 0.55 | 0.17 | 0.64 | 0.13 |
| Total visit duration to self (second 4) | 0.58 | 0.17 | 0.64 | 0.12 |
| Total visit duration to self (second 5) | 0.58 | 0.13 | 0.59 | 0.15 |
| Total visit duration to other (second 2) | 0.64 | 0.13 | 0.58 | 0.12 |
| Total visit duration to other (second 3) | 0.67 | 0.14 | 0.59 | 0.12 |
| Total visit duration to other (second 4) | 0.67 | 0.13 | 0.58 | 0.15 |
| Total visit duration to other (second 5) | 0.68 | 0.12 | 0.57 | 0.10 |

effect of Time Block, $F(3,18) = 3.23$, $p = 0.029$, $\eta_p^2 = 0.15$, and a significant main effect of Type of Stimulus, $F(1,18) = 6.46$, $p = 0.02$, $\eta_p^2 = 0.26$ (**Figure 4**), with PTSD participants spending more time looking at other unknown faces compared to their own face (measured as total eye gaze duration) (other unknown faces M = 0.66, SE = 0.025, own face M = 0.55, SE = 0.028). The interaction was not significant in this group. Planned *post hoc* comparisons indicated that PTSD participants spend less time looking at themselves in second 2 ($t = 2.38$, $p < 0.02$, df = 18), second 3 ($t = 2.08$, $p = 0.05$, df = 18), and second 5 ($t = 2.49$, $p = 0.02$, df = 18).

Finally, to explore hypothesis 4, that there will be a correlation between total eye gaze duration for the self/others and trait self-disgust, we calculated the difference between total eye gaze toward other unknown faces and toward the self (mean other–mean self) and correlated this difference with self-disgust scores. We found a significant positive correlation (Pearson's) $r = 0.31$, $p < 0.05$ suggesting that as self-disgust scores increase the mean total eye gaze away from the self and toward other unknown faces also increases. This finding provides additional evidence for the avoidance hypothesis of self-disgust.

## DISCUSSION

In the present study we investigated, for the first time, self-disgust, loneliness and mental health outcomes in war veterans with PTSD. We also explored the mediating role of self-disgust in the relationship between loneliness and depression and anxiety in veterans with PTSD and non-PTSD individuals from the general population. We hypothesized that war veterans with PTSD would experience higher levels of loneliness, self-disgust, anxiety, and depression compared to the general population. Our findings supported this hypothesis. Specifically, war veterans with PTSD reported higher scores in all the examined variables with large effect sizes following Cohen's conventions (Cohen, 1969; Richardson, 2011). Our second hypothesis stated that self-disgust will mediate the relationship between loneliness and symptoms of anxiety and depression in both groups (Ypsilanti et al., 2019, 2020). This hypothesis was partially supported by our findings. Specifically, in war veterans with PTSD, self-disgust significantly improved predicted variance in anxiety symptoms, over and above the effects of loneliness, and also mediated the relationship between loneliness and anxiety. However, self-disgust did not increase predicted variance in depression symptoms and did not mediate the association between loneliness and depression in war veterans with PTSD. In the non-PTSD participants, self-disgust significantly increased predicted variance in both anxiety and depression symptoms, over and above the effects of loneliness, and significantly mediated the association of loneliness with both depression and anxiety symptoms.

Our findings are largely in support of previous research where self-disgust mediated the association between loneliness and symptoms of depression in the general population

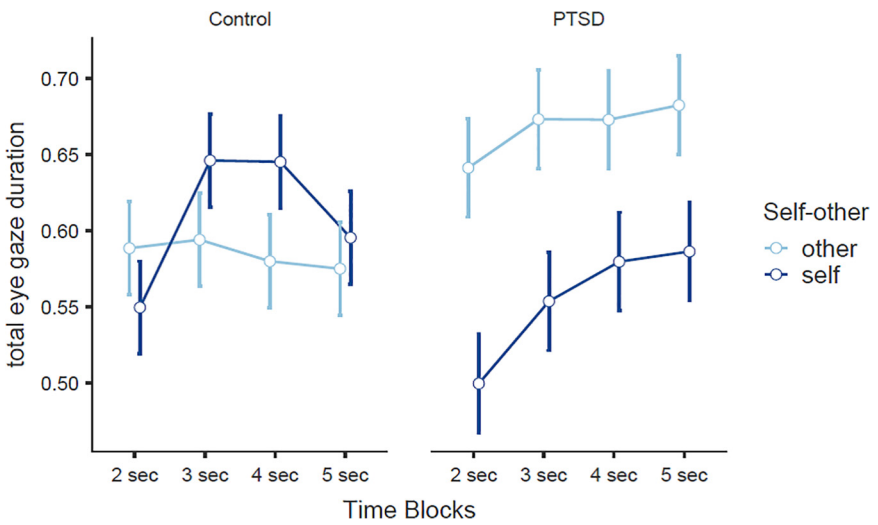


**FIGURE 4 |** Total eye gaze duration across 4 time blocks in war veterans with PTSD and non-PTSD individuals for their own face and the face of an unknown other.

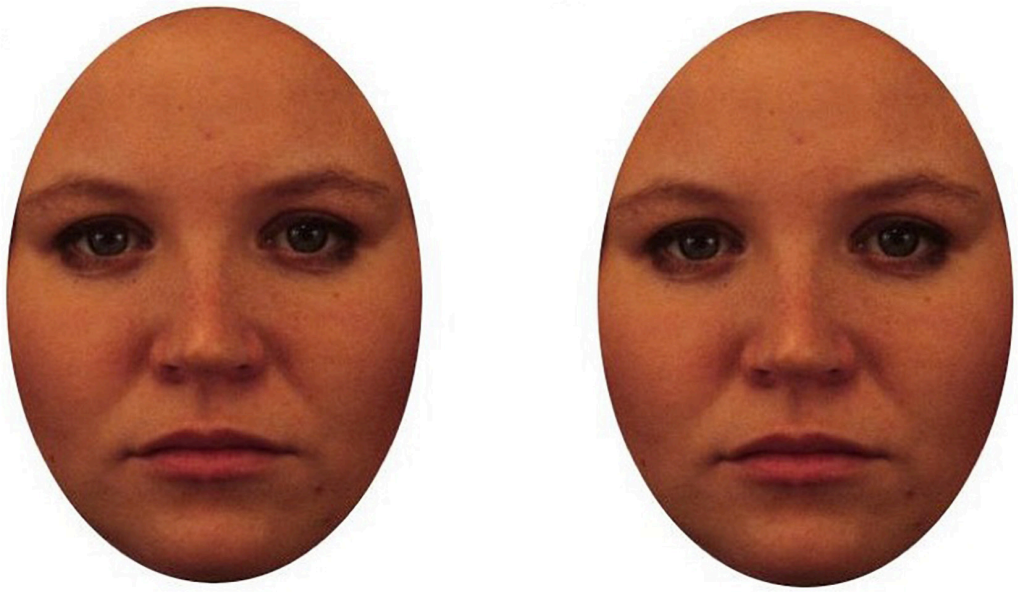

**FIGURE 5 |** Sample of the eye-tracking stimuli from the Karolinska database faces depicting two unknown faces.

(Ypsilanti et al., 2019). The present study also further extends previous research on self-disgust and mental health difficulties (e.g., Brake et al., 2017; Clarke et al., 2019) by showing that self-disgust mediated the association between loneliness and anxiety symptoms in both war veterans with PTSD and a non-PTSD group from the general population. However, the non-significant mediation effect of self-disgust on the loneliness-depression association in the PTSD group is in contrast with previous research where self-disgust prospectively predicted depression (Powell et al., 2013), mediated the relationship between dysfunctional thoughts and depression (Overton et al., 2008), and mediated the relationship between loneliness and depression in the general population (Ypsilanti et al., 2019).

Previous research has also suggested that loneliness induces negative affective states and the tendency to misinterpret social contact as threatening (i.e., social threats), which may enhance social withdrawal and increase negative ruminations toward social interactions (Cacioppo and Hawkley, 2009; Hawkley and Cacioppo, 2010; Cacioppo et al., 2015). Although this has not been directly explored in war veterans with PTSD it is possible that loneliness in this population increases anxiety by creating a negative affectivity loop via self-disgust. This means that rather than experiencing depressive symptoms due to self-disgust (an effect observed in the general population; Overton et al., 2008; Powell et al., 2013), war veterans with PTSD may experience anxiety-related symptoms stemming from negative self-directed emotions. Based on the findings from the present study, we suggest that self-disgust may represent an affective mechanism through which loneliness progresses to the development of anxiety in war veterans with PTSD, but future research is needed to empirically examine this process.

Importantly, in the present study we investigated for the first time the avoidance hypothesis of self-disgust (Powell et al., 2013) in war veterans with PTSD using eye-tracking methodology. For this purpose, we developed a novel task that exposed participants to a picture of their own face alongside a picture of the face of an unknown other. We used time to first fixation as an index of attentional vigilance and found no differences between the two groups (i.e., veterans with PTSD and healthy controls). We used total visit duration across time blocks (2 s, 3 s, 4 s, and 5 s) to examine attentional avoidance following previous research (Armstrong and Olatunji, 2012; Ypsilanti et al., 2020). Our results demonstrated that war veterans with PTSD behave differently when exposed to such stimuli compared to a group of people from the general population. Specifically, veterans with PTSD spent much more time gazing at the faces of unknown other vs. their own face, than people without PTSD. Moreover, this gaze pattern (attentional avoidance) is initiated after the 3$^{rd}$ second of stimulus exposure—as **Figure 4** shows, there is a sharp drop in eye-gaze after 3 s. On the contrary, non-PTSD participants gazed at their own image more time compared to the picture of an unknown other, and did not exhibit avoidance to the self. Specifically, while there is a relatively stable eye-gaze pattern for the image of the unknown other, there is temporarily an increased gaze time at 3 s and 4 s to the image of the self. Taken together, our study shows that veterans with PTSD reported almost three times higher scores in self-disgust, and tended to visually avoid pictures of themselves (vs. others) at later exposure times. Further, the significant positive correlation between total visit duration and self-disgust scores in PTSD participants (Hypothesis 4) suggests that this eye-gaze pattern is, at least partly, related to higher self-disgust scores. Based on previous reports, individuals with high self-disgust avoid their own reflection and direct their eye gaze away for their own image (Ypsilanti et al., 2020). One possible explanation for this pattern of eye-gaze in veterans with PTSD is that their image may serve as a reminder of a negative "self"

that triggers dysphoria and therefore, avoidance acts as a coping mechanism to relief this negative self-perception. In the present study, we used for the first time an eye-tracking task that exposed participants to their own image alongside another unknown face. By doing so, we were able to determine whether eye gaze was directed to the periphery of their own face (outside the area of interest) or toward the face of an unknown other (inside another area of interest) that does not trigger dysphoric emotions. We found that veterans with PTSD preferred to gaze at other people's faces when they avoided their own image rather than look away from faces altogether. Since this is the first time that eye-gaze has been recorded in such an eye-tracking paradigm among veterans with PTSD conclusions should be drawn with caution.

## Strengths and Limitations

Our study has both theoretical and methodological strengths. In terms of theory, we identified a previously unnoticed variable (i.e., self-disgust) that can potentially explain the association between loneliness and anxiety symptoms. This is important for the following reasons. Previous research has shown that self-disgust is implicated in survivors of traumatic experiences (for a review see Clarke et al., 2019) but most of this research dealt with sexual abuse-related trauma, whereas our study is the first to examine self-disgust in combat-related PTSD among veterans. Secondly, our study highlighted the positive association between self-disgust and loneliness, which was found to be stronger among veterans with PTSD than in the general population. Accordingly, our results further emphasized the mediating properties of self-disgust in the association between loneliness and anxiety symptoms in veterans with PTSD—this advances recent research that reported similar findings in older adults (Ypsilanti et al., 2020).

Methodologically, one of the main strengths of the current study is the application of a novel psychophysiological paradigm to attentional vigilance and avoidance in war veterans diagnosed with PTSD - a population that is difficult to access and recruit in basic psychological research. Eye-tracking tasks provide a unique opportunity to identify early and later attentional processing by allowing individuals to naturally dwell of the stimuli. This novel task exposed participants to their own face alongside an unknown face, to explore whether avoidance would take place (Powell et al., 2013). Presenting two faces simultaneously on the screen allowed us to determine whether eye gaze avoidance was detected in the periphery of their own face or whether there was a more conscious preference to gaze at an unknown other. Another strength of our study is the counterbalanced order of the eye-tracking task and the completion of the questionnaires. This was done to avoid any priming effects that the questionnaires would have on the eye-tracking task.

We also acknowledge several limitations that could be overcome in future research. Firstly, the cross-sectional design limits our potential to make causal inferences about the association between loneliness, self-disgust, and mental health outcomes in PTSD and non-PTSD adults. Longitudinal studies could potentially determine the temporal association between these variables and indicate whether loneliness precedes self-disgust in the genesis of anxiety and depression. It is also important to note that in the present study we did not use war veterans without PTSD as a control group against war veterans with PTSD. Given that our intention was to replicate the mediating role of self-disgust on the associations of loneliness with depression and anxiety symptoms in the general population that was recently reported in the literature (Ypsilanti et al., 2019, 2020), we selected participants without PTSD from the general population as a comparison group.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Sheffield Hallam University Ethics Review Committee. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

AY conceived the idea of the study, contributed to the design and data analysis, and authored the manuscript. RG designed the tasks, recruited and collected all the data, and contributed to that data analysis. LL contributed to the data analysis and co-authored the manuscript. AR contributed to the design of the task and data analysis. PP contributed to the data analysis and edited the revisions of the manuscript. PO contributed to the data analysis and edited the revisions of the manuscript. All authors contributed to the article and approved the submitted version.

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# Addressing Suicide in the Veteran Population: Engaging a Public Health Approach

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Suicide is a national public health issue in America, and it disproportionately affects those who are serving or who have served in the United States military. The US Department of Veterans Affairs (VA) has made suicide prevention its number one clinical priority. VA is committed to prevent suicide among the entire population of those who have served our country in the military, regardless of whether they make use of any VA services or benefits. Suicide can be prevented through the application of a public health strategy embracing partners at all levels. Following a national strategy, VA has embarked on an effort involving the application of a public health strategy combining both clinically-based and community-focused interventions. This paper describes several examples of these efforts and steps forward.

**Keywords: suicide prevention, suicide intervention, Public health approach, veterans, Department of Veterans Affairs**

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## INTRODUCTION

In 2017, 6,139 veterans died by suicide (1). These veterans were among the over 45,000 Americans who died by suicide during that same year. Suicide is not caused by any one factor, nor can suicide be prevented by application of any one strategy (2, 3). While mental health concerns comprise particular risk factors for suicide, larger societal issues also serve as additional unique risk factors for suicide (e.g., homelessness, financial concerns, relationship distress, unemployment, increasing alcohol sales, and increasing sales of and access to firearms). Our national strategies must not only include clinically-based intervention strategies, but also proactive community-based prevention efforts to also address these broader factors. In 2018, VA published a national strategy for preventing Veteran suicide (4) followed in 2019 by the publication of the revised VA-DoD Clinical Practice Guideline on the Assessment and Management of Patients at Risk for Suicide (5). These documents provide overarching guidance for the vision and implementation of VA's national suicide prevention initiative.

## WHAT WE KNOW FROM THE DATA

Since 2014, VA has published an annual report on suicide death data among veterans. The primary purpose of veteran suicide data reporting is to provide critical information to move suicide prevention efforts forward. The VA creates state data sheets as a companion to the national report to prompt local/ regional action (6). The annual report is based upon a close collaboration with the Department of Defense (DoD) and the Centers for Disease Control and Prevention (CDC). VA and DoD partners complete searches of the National Center for Health Statistics' National Death Index (NDI), the national gold standard of all individuals who

have died to identify all individuals who are veterans, which is compiled annually by the CDC based-upon national suicide mortality data reported to the CDC by each state and US territory. NDI data is typically released 11 months after the end of a calendar year and then followed by this extensive detailed review for veterans, which takes significant time to ensure information accuracy. For example, the 2019 National Suicide Prevention Annual Report was published in September 2019, and it included the suicide death data for Veterans between 2005 and 2017 with the reporting period ending on December 31, 2017 (1).

The report contains information on counts, measures of central tendency, and rates broken down by age, gender, means of death, and a few additional key variables. In 2005, an average of 87 American adults (including an average of 16 veterans) died by suicide each day. In 2017, an average of 124 Americans died by suicide each day (including an average of 17 veterans). However, given the decline in the veteran population during that time period, the suicide rate for veterans in 2017 was 1.5 times higher than the rate for non-veteran adults (2.2 times higher among female veterans than non-veteran women, and 1.3 times higher among male veterans than non-veteran males). The highest rate of suicide among veterans is among male veterans between the ages of 18 and 34, but the highest number of suicides among veterans is among male veterans age 55 and older. Nearly 70% of veteran suicide deaths (69.4%) resulted from a firearm injury which is higher than among non-veteran adult suicide deaths (48.1%).

## FOUNDATIONAL COMPONENTS OF VA'S SUICIDE PREVENTION INITIATIVE: THE NATIONAL STRATEGY, THE VA/DoD CLINICAL PRACTICE GUIDELINE, AND RESEARCH

National Strategy for Preventing Veteran Suicide (4) provides a framework for identifying priorities, organizing efforts, and leading a national effort to prevent veteran suicide over the next decade. It aligns with the 2012 National Strategy for Suicide Prevention and the strategy published by the Department of Defense. The National Strategy contains four strategic directions, 14 goals, and 43 specific objectives, all framed within a public health approach. The national strategy is built upon the National Academy of Medicine model of having actions focused on the entire population (Universal), those known to be at higher risk (Selective), and those known to be at highest risk (Indicated). The national strategy leverages the systems within which veterans typically live—families, communities, healthcare systems, workplaces, schools, faith-based and other social groups—to ensure all veterans are reached, both inside and outside of the VA system.

In 2013, the VA and DoD published the first clinical practice guideline (CPG) for the assessment and management of patients at risk for suicide. A revised and updated CPG, the VA/DoD Clinical Practice Guideline for the Assessment and Management of Patients at Risk for Suicide, was published in 2019 and is based upon a thorough review of the existing literature at the time of publication (5). The CPG is intended to guide clinical decision-making at critical points in the identification and management of suicidal behavior. The CPG identifies essential features and potential actions for both those at acute risk and at chronic risk. The CPG contains five recommendations on screening and evaluation, including three that VA currently uses as part of its comprehensive suicide risk screening and evaluation program. It also contains 12 recommendations on risk management and treatment, including several items that VA currently implements at its health care facilities.

## VA'S PUBLIC HEALTH APPROACH

To accomplish VA's goal of reducing suicide among all 20 million U.S. Veterans, a comprehensive public health approach that blends clinically-based interventions and community-based prevention strategies is needed (See **Figure 1**, National, State, Community Program Coordination). VA is currently deploying both strategies, with high level examples described below, to ensure the fullest implementation of the public health approach to suicide prevention across the nation.

## EXAMPLES OF VA'S CLINICALLY-BASED INTERVENTIONS

Promoting evidence-based clinical strategies are a key component to suicide prevention. Clinically-based strategies rely upon a foundational level of staffing to ensure success. Mental health staff enhancements have been associated with decreases in suicide rates among VHA patients in regions where the increases in mental health outpatient staffing were greatest (7). In order to promote maximum success of clinically-based interventions for suicide prevention in alignment with the evidence-base, VA is striving to reach recommended staffing levels. This includes a minimum outpatient mental health staffing ratio of 7.72 outpatient mental health full time employee equivalent (FTE) staff to 1,000 veterans in outpatient mental health and a national minimum benchmark for suicide prevention staffing at 0.1 suicide prevention coordinators/case manager FTEE per 1,000 veterans enrolled at a facility. Below we outline a few examples of clinically-based interventions deployed nationally in VA as part of the strategic plan for suicide prevention.

### Universal Screening

Identifying veterans at risk for suicide prior to a time of crisis is a critical factor in the deployment of VA's national strategy. The implementation of universal screening for suicide has a strong evidence-base (5). In 2018, VA launched the largest standardized suicide risk screening and assessment process in the country, known as the Suicide Risk Identification Strategy (Suicide Risk ID) which includes a first and second level screens followed by a comprehensive suicide risk evaluation as indicated. The population-based mental health screening process is implemented for those with unrecognized risk (universal), for those who may be at risk (selected), and for those at elevated risk (indicated). When initial screening is positive, veterans are provided with a comprehensive suicide risk evaluation. For

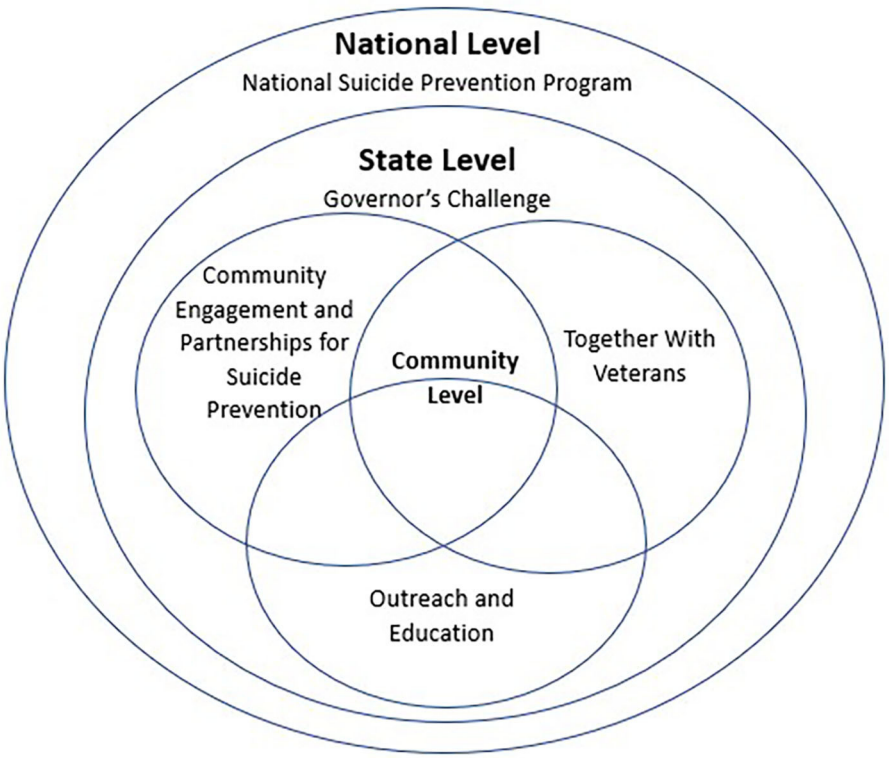


**FIGURE 1 |** National, state, community program coordination.

veterans presenting to other VHA services VA has setting specific guidance for screening and assessment. Between October 1, 2018, and March 2, 2020, 4,533,105 veterans have been screened for suicide across the VHA in all ambulatory settings. Veterans identified at risk through this process are then connected with services to get them the care they need when they need it.

## Safety Planning in the Emergency Department

One advantage of working in a large health care system is the ability to deploy innovation at a rapid pace. One such example is the deployment of Safety Planning in Emergency Departments (SPED). National VA leaders were inspired about initial research findings on safety planning and follow-up caring contacts for those seen in emergency department settings (8). Through implementation of this program, Stanley et al. (8) found a reduction in suicidal behaviors by almost half (45%) in the 6 months following emergency department visits. VA quickly implemented across the entire VA health care system and SPED was born. When a veteran presents to the emergency department or an urgent care center and is assessed as being at risk of suicide, but still safe enough to be discharged home, VA deploys a suicide safety planning intervention, including lethal means safety counseling, while the person is still in the emergency department or urgent care center. After discharge, the individual veteran is then personally contacted through regular outreach calls to facilitate engagement in outpatient mental health care. Ongoing calls are made until the Veteran is engaged in mental health care. Currently SPED is now being rolled out across all 140 health care systems.

## Recovery Engagement and Coordination for Health—Veterans Enhanced Treatment (REACH-VET)

In collaboration with the National Institute of Mental Health, VA developed REACH-VET, a clinical program based upon VA's electronic health record system using predictive analytics to identify veterans at the highest statistical risk for suicide in order to engage outreach and prevention efforts (9, 10). Monthly, local points of contact receive list of veterans deemed to be at highest risk for suicide. Clinical providers then provide personal outreach to each individual veteran to ensure all needed care is provided and treatment plans are reviewed (11). Initial validation studies highlight how this approach identifies veterans with 30–60 times higher rate for suicide, providing a potential mechanism for earlier intervention prior to a time of crisis. Full program evaluation efforts are underway to continue to study outcomes from this national rollout. Progress is tracked monthly and a technical assistance is provided to facilities facing challenges in implementation.

## Same Day Access

Connecting veterans to care the same day as services is needed is a critical component of suicide prevention. As part of the My

VA Access Initiative, VA established same day mental health and primary care services across the nation in 2017. The My VA Access Initiative also included a larger emphasis on expanded implementation of Primary Care Mental Health Integration (PCMHI) which is one method of providing same day access to mental health services as part of routine primary care, reducing stigma, and increasing timeliness of service delivery. PCMHI has been shown to reduce wait times for mental health services, increase odds of attending future appointments, and lower no-show rates for appointments (12–15). It also provides an opportunity to deliver mental health services to those who may otherwise not seek them and to identify, prevent, and treat mental health conditions at the earliest opportunity. This is an important ingredient in suicide prevention because research has shown that 45% of individuals (16) who die by suicide have contact with a primary care provider (PCP) in the month prior to their death.

### Veterans Crisis Line

In addition to providing same day access to services at VA facilities, the Veterans and Military Crisis Line (VMCL) connects Veterans in crisis with qualified, caring VA responders through a confidential toll-free hotline, online chat, or text 24 h/7days/week. VMCL engages ∼1,850 calls per day, sees an additional 300 contacts through chat and text programs, and offers ∼360 referrals per day to local VA Suicide Prevention Coordinators who contact Veterans to ensure continuity of care with local VA providers. VMCL consistently exceeds performance targets. In 2019, VCL responders answered 96.82% of calls in 20 s or less with an average speed of 9.92 s, maintained an abandonment rate of 2.78%, had a rollover rate of 0.027% which was a 98% reduction in rollovers from FY18.

## EXAMPLES OF VA'S COMMUNITY-BASED PREVENTION STRATEGIES

Of the 17 veterans who die by suicide every day, nine have never received VHA services and two have not received VHA services within the last 2 years. Moving upstream and reaching outside VA's walls to engage veterans in the community in lifelong health, well-being, and resilience is a critical part of VA's National Strategy. Community prevention focuses addressing social determinants of health outside the VHA healthcare system to promote early awareness and prevention prior to times of crisis, while also expanding collaboration and coordination of services across all veterans, families, Non-VHA healthcare systems, other community partners, and the VA. Community-based interventions are science-based approaches to changing community systems and contexts to improve population health outcomes (17), and these have been shown to effectively reduce suicide rates in diverse communities around the world (18). Three examples of community prevention models that have shown promise, Governor/ Mayoral Challenges VISN Community Prevention Pilots, and Together with Veterans are outlined below. VA is currently actively deploying all three and supports them with technical assistance. The interrelation among these programs is seen in the figure.

### Governor's and Mayor's Challenges

In 2018, VA partnered with the Substance Abuse and Mental Health Service Administration (SAMHSA) to launch Mayor's Challenge and in 2019 it expanded these efforts to launch the Governor's Challenges. These challenges engage both government and community partners in the development of regionally developed interagency strategic plans to address veteran suicide through the deployment of evidence-based strategies. The Mayor's Challenge currently consists of 24 cities and counties. Since the program's inception in 2019, seven states have joined the Governor's Challenges and the program is expanding to 28 additional states over the next 2 years and then with a final goal of engaging all 50 states. City and states are provided with technical assistance and support through site visits, policy academies, and virtual consultation to enhance their plans and incorporate evidence-based strategies to reach out to all veterans in their local areas to prevent suicide, pairing state-level policy makers with local leaders to implement comprehensive plans.

### VISN Community Prevention Pilots

Over the past year, the Office of Mental Health and Suicide Prevention partnered with Veterans Integrated Service Network (VISN) 23 in developing a pilot program to promote community prevention strategies to reach veterans through community engagement and partnerships focused upon coalition building at the local level. Implementation scientists from the University of Pittsburgh's Program Evaluation and Research Unit (PERU) and VA leadership worked collaboratively to provide technical assistance and facilitation hire and support 10 Community Engagement and Partnership Coordinators (CEPCs). CEPCs supplement the work of VA's 450+ suicide prevention coordinators by focusing on expanding community efforts to increase awareness of veteran suicide and moving awareness to engagement of local coalitions to implement community-focused evidence-based suicide prevention strategies. The CEPCs will collaborate at the community, regional, and state levels, to implement community partnerships, Together with Veterans, and the Governor's Challenge. Program evaluation efforts are now underway with planned expansion to three other VISNs this year, with an ultimate goal of engaging all 18 VISNs.

### Together With Veterans (TWV)

TWV is a community-based suicide prevention program for rural Veterans (19), which is focused upon partnering rural veterans and their communities to implement community-based suicide prevention. Based in implementation science, TWV assists veterans in the community in implementing evidence-based suicide prevention strategies to reach rural veterans. TWV is a VA Office of Rural Health program focused on empowering and supporting Veteran to Veteran coalition building. This includes efforts to increase lethal means safety, gatekeeper training, training of primary care providers, stigma reduction and help-seeking behavior promotion, increasing access to crisis services, and enhancing efforts to support veterans at highest risk for suicide (19). Currently, TWV is deployed in several rural regions with additional sites being added the 2020 calendar year.

## DISCUSSION

Suicide prevention is the top clinical priority for VA and a priority for public health across the globe. VA has embarked on a comprehensive program of clinically-based and community-based strategies within a public health framework guided by the research currently available. The above strategies are just a few examples of VA's overarching plan to employ a public health model in the deployment of Suicide Prevention 2.0 over the coming decade combined with specific strategies for implementation now to not only prevent death, but engage Veterans on a journey of health, well-being, and resilience throughout the course of their lifetime. A critical aspect of Suicide Prevention 2.0 is a simultaneous, comprehensive evaluation of its impact, addressing quality, accountability, integrity, and effectiveness, and VA is committed to a transparent assessment and how this compares with initiatives in other sectors. Although suicide prevention is a core responsibility for VA and for all healthcare systems, the mission of suicide prevention cannot be fully achieved by any system. This is an urgent matter that requires a broad public response but one that is adapted to each individual circumstance. There will never be a "one and done" solution. The programs and initiatives outlined in this paper represent the current iteration of VA's committed effort to prevent suicide, but there is much more to learn and to do and for that we need to respond as a nation in recognition and gratitude for the service given by all those who are veterans.

## AUTHOR CONTRIBUTIONS

DC: principal author, outlined, and drafted manuscript. LK and MM: edited and contributed content. All authors contributed to the article and approved the submitted version.

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REVIEW
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# The National Health and Resilience in Veterans Study: A Narrative Review and Future Directions

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United States (U.S.) veterans are substantially older than their non-veteran counterparts. However, nationally representative, population-based data on the unique health needs of this population are lacking. Such data are critical to informing the design of large-scale outreach initiatives, and to ensure the effectiveness of service care delivery both within and outside of the Veterans Affairs healthcare system. The National Health and Resilience in Veterans Study (NHRVS) is a contemporary, nationally representative, prospective study of two independent cohorts ($n$ = 3,157 and $n$ = 1,484) of U.S. veterans, which is examining longitudinal changes, and key risk and protective factors for several health outcomes. In this narrative review, we summarize the main findings of all NHRVS studies ($n$ = 82) published as of June 2020, and discuss the clinical implications, limitations, and future directions of this study. Review of these articles was organized into six major topic areas: post-traumatic stress disorder, suicidality, aging, resilience and post-traumatic growth, special topics relevant to veterans, and genetics and epigenetics. Collectively, results of these studies suggest that while a significant minority of veterans screen positive for mental disorders, the majority are psychologically resilient. They further suggest that prevention and treatment efforts designed to promote protective psychosocial characteristics (i.e., resilience, gratitude, purpose in life), and social connectedness (i.e., secure attachment, community integration, social engagement) help mitigate risk for mental disorders, and promote psychological resilience and post-traumatic growth in this population.

**Keywords: veterans, mental health, aging, genetics, resilience (psychological), EPI—epidemiology**

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## INTRODUCTION

Nationally representative epidemiological studies of United States (U.S.) military veterans conducted outside of the Veterans Affairs (VA) healthcare system are sparse, yet highly valuable, given that only about half (48%) of veterans utilize any VA healthcare services (1), and even fewer (∼20%) utilize VA care as their primary source of health care (2). Moreover, utilization of VA healthcare services is driven by many factors, such as sex, race, income, marital status, and physical and mental health conditions (1, 2). Thus, it is critical to understand the unique needs of veterans at a broader population level to better inform the design of large-scale outreach initiatives and to help ensure the effectiveness of service care delivery.

Further, while a substantial body of research on veterans has focused on risk factors for prevalent mental and physical health conditions, few studies have assessed potentially modifiable factors that may help mitigate risk for these conditions, such as gratitude, social support, optimism, community integration, and purpose in life (3, 4). Accordingly, the overarching goal of the National Health and Resilience in Veterans Study (NHRVS) is to characterize the longitudinal trajectories of mental and physical health outcomes in U.S. veterans, and to study genetic and environmental risk and protective factors that contribute to these trajectories. The NHRVS is a large, nationally representative prospective study which consists of two separate cohorts of 3,157 and 1,484 U.S. military veterans. Additionally, the NHRVS utilizes well-validated measures to examine longitudinal changes of mental and physical health outcomes in this population.

Since the NHRVS began in 2011, it has yielded a total of 82 publications. In this review, we summarize the main findings of all NHRVS studies published as of June 2020, and discuss the broader clinical implications, limitations and future directions of this study. To thematically organize the content, the 82 articles were sorted into six major topic areas: post-traumatic stress disorder, suicidality, aging, resilience and post-traumatic growth, special topics relevant to veterans, and genetics.

# METHODS

## Methodology for National Health and Resilience in Veterans Study

The NHRVS cohorts were recruited to complete a 60-min online survey from a research panel of over 50,000 households that was developed and maintained by GfK Knowledge Networks, Inc. (now Ipsos). GfK Knowledge Networks, Inc. recruited panel members through national random samples by telephone and postal mail. Internet and computer hardware access are provided if needed. GfK Knowledge Networks, Inc. uses dual sampling frames to recruit participants and offers coverage of ∼98% of U.S. households. These sampling procedures are different from Internet convenience panels (i.e., "opt in" panels) as it included listed and unlisted telephone numbers, telephone and non-telephone households, cell-phone-only households, and households with and without Internet access. Only individuals sampled through these probability-based techniques are eligible to participate in the survey. To promote generalizability of results to the entire population of U.S. veterans, post-stratification weights based on demographic distributions of US veterans from concurrent US Census data (5) were applied. Of the 4,750 veterans who were in the survey panel at the time the first cohort (Cohort one; C1) was fielded, 3,408 (71.7%) completed a screening question to confirm their study eligibility (current or past active military status). Of these veterans who completed the screening question, 3,188 (93.5%) confirmed their current or past active military status, and 3,157 (92.6%) completed the survey.

C1 completed a baseline survey in 2011, which included comprehensive measures of demographics and military history, medical and psychiatric status, and psychosocial functioning. Following the baseline survey, 2-, 4-, and 7-year follow-ups were conducted. Wave 2 ($n$ = 2,157; 68.3%) data were collected in 2013, Wave 3 ($n$ = 1,538; 48.7%) in 2015, and Wave 4 ($n$ = 1,310; 41.5%) in 2018. Additional saliva samples were collected from 500 veterans in Wave 3 for epigenetic and telomere length assays. At baseline, C1 was 90.6% male, 76.2% White, 9.6% Black, 8.2% Hispanic, 1.5% mixed races, and the mean age was 60.3 ($SD$ = 15.0, range = 21–96), with 57.3% aged 60 years or older. Two-thirds of participants (66.7%) had completed at least some college education, 75.6% were married/cohabitating, 44.0% reported a household income of $60,000 or greater, 43.5% were retired, and 40.7% reported working part-time and/or full-time. The majority of did not serve in a combat or war zone (65.2%), and 19.3% reported using VA healthcare as their main source of health care.

Cohort 2 (C2) completed a baseline survey in 2013 and a follow-up survey 3 years later. A total of 1,602 individuals responded "Yes" to an initial screening question that confirmed veteran status and 1,484 participated, resulting in a response rate of 92.6%. C2 consists of 1,484 veterans who completed a baseline survey and 713 (48.0%) who completed a 3-year follow-up survey. Veterans in C2 were demographically similar to C1, with 89.7% male, 75.4% White, 9.7% Black, 9.1% Hispanic, and 1.4% mixed races, with a mean age of 60.4 ($SD$ = 15.3, range 20–94) at baseline. The majority of C2 veterans were married/cohabitating (70.1%), 44.2% were retired, and 41.6% were working part-time and/or full-time, and had household incomes of $60,000 or greater (43.4%); two-thirds (66.9%) had completed at least some college education. The majority of C2 veterans did not serve in a combat or war zone (61.6%), and 21.3% reported using VA as their main source of healthcare. Saliva samples were also obtained from both NHRVS cohorts, with genetic data (PsychChip) available for 2,827 veterans.

## Review Methodology

A search of Pubmed and Scopus was conducted with the terms, "National Health and Resilience in Veterans Study"; "NHRVS"; "nationally representative sample of U.S. veterans"; "U.S. veteran population"; and the author/principal investigator "Pietrzak, R.H." Non-NHRVS studies were excluded if "residential treatment"; "National Epidemiologic Survey on Alcohol and Related Conditions"; "Million Veteran Program"; or "VA cooperative study 504" were in the title/abstract. This search revealed 90 studies, 8 of which were excluded for not utilizing NHRVS data upon further review. The final review included 82 original research studies.

# POST-TRAUMATIC STRESS DISORDER

Eighteen studies (see **Table 1**) utilized data from the NHRVS to examine the prevalence and risk factors for PTSD and co-occurring conditions in veterans, as well as the factor and network structure of PTSD symptomatology. Below, we summarize results of these studies.

## Prevalence

PTSD is one of the most prevalent mental disorders among U.S. veterans. Prevalence estimates of this disorder among veterans ranging widely (23, 24), partly due to most studies being

**TABLE 1 |** Post-traumatic stress disorder.

| Citation | Title | Sample | Findings | Clinical implications |
|---|---|---|---|---|
| Wisco et al. (6) | Post-traumatic stress disorder in the US veteran population: Results from the National Health and Resilience in Veterans Study | Cohort 1 ($n = 3,157$) | The prevalence of lifetime and current PTSD was 8.0 and 4.8%, respectively, and PTSD was associated with elevated risk for mood, anxiety, suicidality, and substance use disorders. | Protective characteristics such as resilience, community integration, and secure attachment style, were associated with decreased risk for PTSD, thereby suggesting the importance of potentially targeting these factors in prevention and treatment efforts. |
| Armour et al. (7) | Dimensional structure of DSM-5 post-traumatic stress symptoms: Support for a hybrid anhedonia and externalizing behaviors model | Cohort 2 ($n = 1,484$) | A new 7-factor model of DSM-5 PTSD symptoms was found to be a superior fit compared to 5 other models ranging between 4- and 6-factors of PTSD. | Identifying the optimal dimensional representation of PTSD symptoms can help inform the etiology of PTSD, and comorbidity between PTSD and other psychiatric disorders. |
| Pietrzak et al. (8) | Functional significance of a novel 7-factor model of DSM-5 PTSD symptoms: Results from the National Health and Resilience in Veterans study | Cohort 2 ($n = 1,484$) | Differential patterns of associations were observed between 7 DSM-5 PTSD symptom clusters, and psychiatric comorbidities, suicidal ideation, hostility, and functioning and quality of life. | Results suggest that a 7-factor hybrid model of DSM-5 PTSD symptoms provides greater specificity in regards to how the phenotypic expression of PTSD symptoms relates to comorbidities, suicidality, hostility, and functioning and quality of life. |
| Tsai et al. (9) | Dissociative subtype of DSM-5 post-traumatic stress disorder in U.S. veterans | Cohort 2 ($n = 1,484$) | 19.2% of veterans with lifetime PTSD and 16.1% of veterans with past-month PTSD screened positive for the dissociative subtype. Those with the dissociative subtype reported more severe PTSD symptoms, comorbid depressive and anxiety symptoms, alcohol use problems. | It is clinically relevant to identify veterans with the dissociative subtype of PTSD, as they reported higher levels of depression, anxiety, alcohol problems, hostility, and PTSD symptoms. |
| Tsai et al. (10) | Dimensional structure of DSM-5 post-traumatic stress disorder symptoms: Results from the National Health and Resilience in Veterans Study | Cohort 2 ($n = 1,484$) | 5.2% of veterans screened positive for past-month PTSD and a new 6-factor model of DSM-5 PTSD symptoms was found to provide the best dimensional representation of PTSD symptom clusters and demonstrated validity in assessing health outcomes. | Findings suggest the 6-factor model of PTSD symptoms may provide a more refined phenotypic model of PTSD than the 4-factor DSM-5 model, and may have utility in understanding the etiology of PTSD, personalization of treatment, and monitoring of treatment outcomes. |
| Contractor et al. (11) | Latent profiles of DSM-5 PTSD symptoms and the "Big Five" personality traits | Cohort 2 ($n = 1,226$) | Comparing all classes to the most severe PTSD class, most differences were found for utilization of mental health treatment; and the preferred use of self-distraction, denial, active coping, emotional and instrumental support, and behavioral disengagement coping strategies. | Findings underscore the importance of considering personality pathology in examining the heterogeneity of PTSD symptom presentation, as typologies differed in relation to mental healthcare utilization, coping strategies, and substance use. |
| Mota et al. (12) | Late-life exacerbation of PTSD symptoms in US veterans: Results from the National Health and Resilience in Veterans Study | Cohort 1 Baseline ($n = 2,119$) and Wave 2 ($n = 1,441$) | Approximately 1 in 10 older US veterans experienced a clinically significant exacerbation of PTSD symptoms in late life. Executive dysfunction may have contributed to risk for exacerbated PTSD symptoms. | Results underscore the importance of routine assessment and monitoring of PTSD symptoms, particularly anxious arousal, in aging veterans, even among those who have not previously been symptomatic. |
| Mota et al. (13) | High burden of subthreshold DSM-5 post-traumatic stress disorder in U.S. military veterans | Cohort 2 ($n = 1,484$) | Approximately one in three US veterans experienced clinically significant PTSD symptoms in their lifetime. Further, subthreshold PTSD was associated with elevated comorbid psychiatric disorders, as well as decrements in mental and physical functioning. | Results underscore the importance of assessment, prevention and treatment efforts in targeting veterans and other trauma-affected individuals clinically elevated PTSD symptoms that are below the threshold for a diagnosis of PTSD. |
| Wisco et al. (14) | Probable post-traumatic stress disorder in the US veteran population according to DSM-5: Results from the National Health and Resilience in Veterans Study | Cohort 2 ($n = 1,484$) | The prevalence of DSM-5 probable PTSD, conditional probability of probable PTSD, and odds of psychiatric comorbidity were similar to prior findings with DSM-IV-based measures in US veterans. | Findings indicate that veterans should be assessed for a wide range of both military and non-military trauma when screened for PTSD, and highlight the high rates of comorbid PTSD and other mental disorders. |
| Armour et al. (15) | A network analysis of DSM-5 post-traumatic stress disorder symptoms and correlates in U.S. military veterans | Cohort 2 ($n = 221$) | The 20-item DSM-5 PTSD network demonstrated that the most central symptoms were negative trauma-related emotions, flashbacks, detachment, and physiological cue reactivity. | Specific intrusive, negative cognition and mood, and hyperarousal symptoms are central to the PTSD symptom network in symptomatic veterans. Interventions targeting these symptoms may help mitigate chronicity of this disorder. |

*(Continued)*

**TABLE 1** | Continued

| Citation | Title | Sample | Findings | Clinical implications |
|---|---|---|---|---|
| Claycomb Erwin et al. (8) | The 7-factor hybrid model of DSM-5 PTSD symptoms and alcohol consumption and consequences in a national sample of trauma-exposed veterans | Cohort 2 ($n = 916$) | CFA results indicated an excellent fit for the combined CFA model of the 7-factor hybrid model of PTSD and two-factor AUDIT model. Lifetime dysphoric arousal, negative affect, and anhedonia symptom clusters were most strongly associated with past-year alcohol consequences. | Results highlight the need to assess for alcohol-related consequences in veterans with internalizing PTSD symptoms, and underscore the importance of assessing beyond mere alcohol consumption to the adverse consequences of alcohol use. |
| Wisco et al. (16) | A comparison of ICD-11 and DSM criteria for post-traumatic stress disorder in two national samples of U.S. military veterans | Cohort 1 ($n = 3,157$) and Cohort 2 ($n = 1,484$) | A significantly greater proportion of veterans met criteria for lifetime and past-month PTSD under DSM-IV/5 than under ICD-11. 21.8–35.9% of those who met criteria under DSM IV/5 did not meet under ICD-11, whereas only 2.4–7.1% of those who met under ICD-11 did not meet under DSM-IV/5. | Of the estimated 1.3 million U.S. veterans with a lifetime history of DSM-5 PTSD, over 280,000 (22%) would not meet ICD-11 criteria and these individuals might not have access to the same healthcare, disability benefits, and other important services that they would under DSM-5 |
| Wolf et al. (17) | The Dissociative Subtype of PTSD Scale: Initial evaluation in a national sample of trauma-exposed veterans | Resampled subset from Cohort 1 ($n = 860$) | Of the veterans with possible lifetime PTSD, nearly 40% of were included in the subtype. Items assessing derealization and depersonalization were the strongest indicators of the dissociative subtype. | Derealization/depersonalization on the DSPS has the potential to identify individuals with the dissociative subtype of PTSD, while the amnesia and loss of awareness subscales may provide useful supplemental Information about current symptoms. |
| von Stockert et al. (18) | Evaluating the stability of DSM-5 PTSD symptom network structure in a national sample of U.S. military veterans | Cohort 2 Baseline and Wave 2 ($n = 611$) | PTSD symptoms at Time 1 and Time 2 using the DSM-5 PTSD symptom network structure did not differ significantly with regard to network structure or global strength. | Findings suggest that trauma-related avoidance, intrusive, and dysphoric symptoms may contribute to the chronicity of PTSD symptoms in veterans. |
| Byrne et al. (19) | Latent typologies of DSM-5 PTSD symptoms in U.S. military veterans | Cohort 2 ($n = 158$) | A three-class solution was determined, with Dysphoric (36.2%), High Symptom (34.0%), and Threat (29.8%). Threat had greater intrusions and avoidance; Dysphoric had greater negative affect. The High Symptom typology had high probabilities of all symptoms. | The three identified PTSD typologies were differentially linked to clinical and trauma characteristics. These findings underscore the importance of a personalized approach to the assessment and treatment of DSM-5 PTSD. |
| Kachadourian et al. (20) | Post-traumatic stress disorder symptoms, functioning, and suicidal ideation in US military veterans: A symptomics approach | Cohort 2 ($n = 1,484$) | Nonspecific anhedonic and hyperarousal symptoms of PTSD were most strongly associated with measures of physical and mental functioning, quality of life, and suicidal ideation. | Interventions targeting non-specific anhedonic/internalizing and irritability and aggression symptoms of PTSD may be useful in mitigating suicidal ideation, and promoting functioning and quality of life in veterans. |
| McCarthy et al. (21) | Self-assessed sleep quality partially mediates the relationship between PTSD symptoms and functioning and quality of life in U.S. veterans: Results from the National Health and Resilience in Veterans Study | Cohort 1 ($n = 3,157$) | 27.6% of veterans reported poor sleep quality, with poor sleep quality being significantly higher among veterans who screened positive for probable PTSD. Poor sleep quality partially mediated the relationships between PTSD symptom severity and functioning and QOL measures. | Nearly 1 of 3 U.S. veterans reported poor quality sleep. Assessment and monitoring of sleep difficulties may help mitigate the deleterious effect of PTSD symptoms on functioning and QOL. |
| Herzog et al. (22) | Dissociative symptoms in a nationally representative sample of trauma-exposed U.S. military veterans: Prevalence, comorbidities, and suicidality | Cohort 2 ($n = 1,264$) | 1 in 5 veterans endorsed mild-to-severe dissociative symptoms and veterans with dissociative symptoms had greater psychiatric comorbidity and poorer functioning. Dissociative symptoms predicted suicide risk above other comorbidities and trauma history. | Dissociative symptoms in veterans may be a transdiagnostic risk factor for mental disorders and functional difficulties independent of trauma exposure and PTSD. |

conducted in non-representative samples (e.g., convenience sample of Vietnam-era veterans or veterans deployed to Iraq or Afghanistan). Using data from the NHRVS, which surveyed a nationally representative sample of U.S. veterans, Wisco et al. (6, 14) found that estimates of lifetime DSM-IV and DSM-5 PTSD were 8.0 and 8.1%, respectively, and past-month PTSD were 4.8 and 4.7%, respectively. Further, to understand the burden of subthreshold manifestations of PTSD, Mota et al. (13) analyzed NHRVS data and found that the prevalence of lifetime and current subthreshold DSM-5 PTSD was 22.1 and 13.5%, respectively. These prevalences were markedly higher than prevalences of lifetime and current PTSD (8.0 and 4.5%, respectively) (13).

## Exacerbation/Re-emergence of PTSD in Late-Life

Research on older veterans has also suggested that PTSD symptoms may re-emerge or become exacerbated in older age among trauma-exposed veterans (25). Using NHRVS data, Mota et al. (12) found that nearly 10% of older U.S. veterans

experienced exacerbated PTSD symptoms an average of nearly 3 decades after their worst trauma. Cognitive difficulties, particularly perceived deficits in executive function, were the sole determinant of late-life exacerbation of PTSD symptoms. These findings suggest that late-life exacerbation of PTSD symptoms affects a substantial minority of older veterans in the U.S., and that reductions in executive control may increase risk for this phenomenon.

## Longitudinal Trajectories of PTSD Symptoms

A recent study (26) utilized all four waves of data from C1 and found evidence of three predominant courses of PTSD symptoms over a 7-year period: low/no (89.2%), moderate (7.6%), and severe (3.2%). Relative to veterans in the no/low symptom course, those in the moderate and severe courses endured a significantly greater number of lifetime traumatic events, reported greater physical health difficulties, were more likely to have lifetime psychiatric histories; and reported lower social connectedness. Importantly, more than 10% veterans evidenced a symptomatic elevation of PTSD symptoms that steadily declined over a 7-year period. Results suggested that interventions to help bolster social connectedness may help mitigate risk for symptomatic trajectories of PTSD in U.S. veterans.

## DSM-5 vs. ICD-11 Classification of PTSD

The *Diagnostic and Statistical Manual of Mental Disorders* (DSM) and *International Classification of Diseases* (ICD) are the two major diagnostic systems commonly used worldwide and, historically, the two have defined PTSD using similar criteria. However, in the recent publication of the ICD-11 (27), a definition of PTSD was proposed that diverges substantially from DSM-5 and reduces the total number of symptoms to 6, compared to 20 in DSM-5. Therefore, it is important to compare how using different diagnostic definitions of PTSD may impact reported prevalence of the disorder. To evaluate this possibility, Wisco et al. (16) found that using the ICD-11 diagnostic criteria yielded significantly lower estimates of lifetime (6.9 vs. 5.0%) and past-month (4.0 vs. 2.7%) PTSD than DSM-5 criteria, without reducing associations with psychiatric comorbidities. Importantly, among individuals excluded under ICD-11, all endorsed clinically significant distress or functional impairment related to their PTSD symptoms, suggesting that the ICD-11 criteria may underestimate clinically meaningful distress and impairment related to PTSD symptoms (16).

## Dissociative Subtype of PTSD

The DSM-5 formally introduced a dissociative subtype of PTSD, which includes symptoms of depersonalization (i.e., "the experience of being an outside observer of or detached from oneself") and/or derealization [i.e., "the experience of unreality, distance, or distortion; (28)]. Tsai et al. (9) evaluated the prevalence and correlates of this subtype of PTSD in the NHRVS. They found that 19.2 and 16.1% of veterans with a positive screen for lifetime and past-month DSM-5 PTSD, respectively, also screened positive for the dissociative subtype. In 2017, Wolf et al. (17) developed and evaluated the Dissociative Subtype of PTSD Scale (DSPS) using a resampled subset of C1 from the NHRVS, and found that nearly 40% of those who screened positive for lifetime PTSD met criteria for the dissociative subtype. Importantly, dissociative symptoms may not exclusively occur in the context of a PTSD diagnosis. A recent NHRVS study (22) found that 20.8% of trauma-exposed veterans experience dissociative symptoms, even if they do not screen positive for this disorder. Results of this study suggest that dissociative symptoms, independent of a PTSD diagnosis, may be a transdiagnostic risk factor for mental health disorders and poor functioning in veterans (22).

## PTSD Symptoms and Functioning

PTSD deleteriously affects various aspects of functioning, including physical health, quality of life (QOL), and psychosocial functioning. Given that there is considerable variability in PTSD symptom presentation among trauma survivors, analysis of individual symptoms that are associated with measures functioning may provide more nuanced insight into how this heterogeneous syndrome may impact these outcomes. Using NHRVS data, Kachadourian et al. (20) employed a novel "symptomics" approach to identify specific PTSD symptoms linked to functional difficulties in trauma-exposed veterans. They found that the non-specific symptoms of this disorder (e.g., difficulty experiencing positive affect, sleep difficulties, loss of interest) were the strongest correlates of poor functioning and suicidal thinking. Furthermore, McCarthy et al. (21) found that sleep difficulties may partially mediate the relationship between PTSD symptoms, and functioning and QOL.

## Symptom Structure of PTSD

The DSM-5 criteria for PTSD include four symptom clusters of intrusions, avoidance, negative alterations in cognitions and mood, and alterations in arousal and reactivity (28). Tsai et al. (10) found that a 5-factor dysphoric arousal model and a 6-factor externalizing behavior model provided a better fit than the 4-factor model of DSM-5 PTSD symptom clusters in C2 of the NHRVS, with the externalizing behavior model providing the best dimensional representation of the symptom clusters. Expanding on this work, a novel 7-factor hybrid model (7) of PTSD was proposed utilizing NHRVS data. This model incorporated unique features of the 6-factor externalizing behavior model (10) with those of another 6-factor (29) to suggest a 7-factor model of intrusions, avoidance, negative affect, anhedonia, externalizing behaviors, anxious arousal (i.e., hypervigilance, exaggerated startle response), and dysphoric arousal (i.e., sleep and concentration difficulties) symptoms. This more nuanced structural model was found to be the best-fitting structural model of DSM-5 PTSD symptoms in veterans and a sample of university students (7). Since the publication of this 7-factor model of DSM-5 PTSD symptoms, several additional studies in various trauma-exposed samples have found support for this structural model of PTSD [e.g., (30–34)].

Evaluating the underlying structure of PTSD symptoms allows researchers to determine specific sets of symptoms that account for comorbidity of PTSD with other disorders and aspects of functioning. Using NHRVS data, Pietrzak et al. (8) examined

the functional significance of the 7-factor hybrid model with comorbid psychopathology (e.g., depression, anxiety, suicide ideation, hostility) and found differential patterns of associations between PTSD symptom clusters and comorbidities. Specifically, anhedonia symptoms were most strongly related to current depression, reduced mental functioning, and quality of life. Externalizing behaviors were most strongly related to hostility. Further, dysphoric arousal, negative affect, and anhedonia symptom clusters were most strongly associated with past-year alcohol consequences (35).

Data from the NHRVS have also been used to examine latent profiles of DSM-5 PTSD symptoms. One study (19) found a three-class solution, described as Dysphoric (i.e., high probabilities of negative affect and anhedonia symptoms), Threat (i.e., high probabilities of intrusive and avoidance symptoms), and High Symptom (i.e., high probabilities of all PTSD symptoms). A related study (11) found evidence of a 5-class PTSD-personality typology solution, which differed with respect to DSM-5 PTSD symptom cluster severity and several of the "Big Five" personality dimensions. Both studies found that these typologies were differentially related to clinical and trauma characteristics, thus underscoring the importance of considering differential "person-based" manifestations of PTSD symptomatology in personalized approaches to the assessment and treatment of this disorder.

## Network Structure of PTSD Symptoms

Exposure to traumatic events in veterans often involves life-threatening combat, injuries, accidents, loss, or interpersonal violence, such as sexual trauma (6). While initial symptoms, such as trouble sleeping, are considered to be a normal reaction to stress in the short term and many veterans manage to overcome these symptoms over time (36), more persistent symptoms can be debilitating. PTSD is a characterized by heterogeneous constellation of symptoms, including intrusive memories related to the trauma, hypervigilance to and avoidance of trauma-related situations and memories, and negative cognitions and mood (28). Network theory suggests that symptoms are correlated in a syndrome because they directly activate and dynamically interact with each other, rather than because they have a shared origin (15). However, until recently little was known about the network structure of PTSD symptoms.

To address this gap, a network analysis of DSM-5 PTSD symptoms was conducted in participants from C2 of the NHRVS with subthreshold or greater PTSD symptoms. Results revealed that negative emotions related to the trauma, detachment, flashbacks, and physiological reactivity were most central and interconnected within the PTSD symptom network (37). Strong connections were observed between flashbacks and nightmares related to the trauma, hypervigilance and exaggerated startle response, and detachment and restricted affect (37). A follow-up study (18) evaluated the temporal stability of this network structure over a 3-year period to help identify symptoms that contribute to the chronicity of PTSD. Results indicated that the network structure for DSM-5 PTSD was stable over the 3-year period with respect to both network structure and global strength (18). Similar to prior research, avoidance, intrusive, and negative cognition and mood symptoms were among the more central nodes, suggesting these symptoms may contribute to the chronicity of PTSD in symptomatic veterans.

## Clinical Implications

Results of NHRVS studies focused on PTSD suggest that veterans report exposure to a wide range of potentially traumatic events from military and non-military experiences, and a strikingly high proportion of veterans—approximately one in three—experience clinically significant PTSD symptoms in their lifetime, with a significant minority screening positive for PTSD (6, 13, 14). Collectively, these results suggest that sleep, avoidance, intrusive, and dysphoric symptoms may contribute to the chronicity of PTSD symptoms in veterans, and may thus represent important targets in prevention, treatment, and risk reduction efforts (18, 20, 21, 37). Utilizing a 7-factor hybrid model of PTSD symptoms may also provide greater specificity in understanding how PTSD symptoms relate to mental health, functioning, and QOL in U.S. veterans (7, 8). Furthermore, resilience, social support, secure attachment, and community integration are potentially modifiable factors that are linked to decreases in PTSD symptoms and may be targeted in prevention and treatment efforts (6, 26).

# SUICIDALITY

Suicide has been a significant public health problem among veterans for over a decade and is a top clinical priority for the VA. In 2016, the rate of deaths by suicide was 1.5 times greater for veterans than for non-veteran adults, after adjusting for age and gender (38). Numerous studies have examined potential mental and physical health risk factors for suicide in veterans, but less research has sought to identify modifiable protective factors (39). To date, seven studies (see **Table 2**) from the NHRVS have examined the prevalence and correlates of suicidality and identified potential protective factors in the U.S. veteran population.

## Prevalence and Longitudinal Courses of Suicidality

Suicidal ideation (SI) is often a precursor to a suicide attempt or death by suicide. Thus, there is a great need to systematically understand the nature and prevalence of SI over time among veterans. This may provide insight into the predominant patterns and causes of SI, which can help determine targets for prevention and treatment. In 2017, Smith et al. (40) analyzed data from C1 of the NHRVS and found that 13.7% of veterans had chronic, new-onset, or remitted SI over a 2-year period. A key finding was that while mental and physical health problems were risk factors for chronic and onset SI, greater social connectedness (e.g., secure attachment style and perceived social support), was negatively related to these outcomes. Building on this work using 4-year prospective data from C1 of the NHRVS, Pietrzak et al. (41) conducted a prospective cohort study of U.S. veterans without SI at baseline to identify the incidence and baseline determinants of new-onset SI. Results revealed that greater age, higher loneliness, disability in instrumental activities of daily

**TABLE 2 |** Suicidality.

| Citation | Title | Sample | Findings | Clinical implications |
|---|---|---|---|---|
| Smith et al. (40) | Nature and determinants of suicidal ideation among U.S. veterans: Results from the National Health and Resilience in Veterans Study | Cohort 1 Baseline and Wave 2 ($n = 2,157$) | 13.7% of U.S. veterans had chronic, onset, or remitted suicidal ideation. Medical and psychological co-morbidities increase risk of chronic suicidal ideation. Social connectedness was protective for remitted and onset, but not chronic suicidal ideation. | Bolstering social connectedness may be helpful in reducing risk for SI and possibly promoting remission from SI. |
| Pietrzak et al. (41) | Factors protecting against the development of suicidal ideation in military veterans | Cohort 1 Baseline, Wave 2, and Wave 3 ($n = 2,093$) | Decreased risk of suicidal ideation was independently associated with greater social support, curiosity, resilience, and acceptance-based coping. Increased risk of suicidal ideation was associated with loneliness, disability in instrumental daily activities, PTSD symptoms, somatic problems, alcohol use problems, denial-based coping, and higher age. | Greater perceived social support, curiosity, resilience, and acceptance-based coping are modifiable and addressed in contemporary cognitive-behavioral psychotherapies, and thus may be promising targets in prevention efforts designed to mitigate suicide risk in veterans. |
| Wisco et al. (42) | Moral injury in U.S. combat veterans: Results from the National Health and Resilience in Veterans Study | Cohort 2 ($n = 564$) | A total of 10.8% of combat veterans acknowledged transgressions by self, 25.5% endorsed transgressions by others, and 25.5% endorsed betrayal, which were associated with risk for mental disorders and suicidality. | Results underscore the importance of moral injury as a risk factor for mental disorders and suicidality in combat veterans. Treatments addressing moral injury may help mitigate risk for these outcomes. |
| Monteith et al. (43) | Psychiatric and interpersonal correlates of suicide ideation in military sexual trauma survivors: The National Health and Resilience in Veterans Study | Cohort 2 ($n = 115$) | Military sexual trauma survivors who reported more severe psychological distress, hazardous alcohol use, and perceived general disapproval from others were significantly more likely to report suicidal ideation in the past two weeks. Hazardous alcohol use and perceived general disapproval from others were associated with being more likely to report attempting suicide in adulthood. | Assessing alcohol use, beliefs regarding how one is perceived by others after their worst traumatic experience, and current psychological distress may be useful targets of screening when considering suicide risk in MST survivors. |
| Corona et al. (44) | Meaning in life moderates the association between morally injurious experiences and suicide ideation among U.S. combat veterans: Results from the National Health and Resilience in Veterans Study | Cohort 2 ($n = 564$) | Interactions between global meaning in life, transgressions by others, and betrayal experiences were significant. Higher meaning in life was associated with significantly lower likelihood of experiencing suicide ideation at higher levels of transgression by others and betrayal experiences. | Purpose and meaning in life may be intervention targets to help reduce suicide risk for veterans who experienced potentially morally injurious experiences of betrayal and transgressions by others. |
| Kachadourian et al. (45) | Protective correlates of suicidality among veterans with histories of post-traumatic stress disorder and major depressive disorder: Results from the National Health and Resilience in Veterans Study | Cohort 1 ($n = 577$) | Current suicidal ideation was 29.4% and the prevalence of lifetime SA was 28.0% in US veterans. Greater purpose in life, curiosity, and optimism were negatively associated with suicidal ideation. None of the protective correlates were associated with attempt history. | Purpose in life, curiosity, and optimism may help mitigate suicide risk and could be targeted in suicide prevention and interventions efforts in high-risk populations. |
| Straus et al. (46) | Purpose in life and conscientiousness protect against the development of suicidal ideation in U.S. military veterans with PTSD and MDD: Results from the National Health and Resilience in Veterans Study | Cohort 1 Baseline, Wave 2, Wave 3, and Wave 4 ($n = 222$) | Nearly one in three (27.1%) of veterans with PTSD and/or MDD developed suicidal ideation over the 7-years. Racial minority status and lower scores on measures of purpose in life, conscientiousness, and frequency of religious service attendance were independently associated with incident suicidal ideation. | Lower purpose in life and conscientiousness, which are potentially modifiable, explained the vast majority of variance in incident suicidal ideation and may be targeted in suicide prevention efforts in veterans with PTSD and MDD. |

living, PTSD, alcohol use problems, and somatic symptoms, and use of denial-based coping were associated with increased risk for SI. After controlling for these risk factors, greater perceived social support, curiosity, resilience, and acceptance-based coping emerged as significant protective factors for SI, accounting for more than 40% of the total variance in predicting SI risk. These findings underscore the importance of considering both risk and protective factors in population-based suicide risk prevention efforts in veterans.

The risk of suicide is even greater in veterans who have been diagnosed with PTSD and/or major depressive disorder (MDD). A recently published NHRVS study (45) found that 29.4% of veterans with PTSD and/or MDD reported current SI and that 28.0% reported a lifetime suicide attempt. Greater purpose in life, curiosity, and optimism were inversely associated with SI. Subsequently, another study (46) used NHRVS data to prospectively examine how a broad range of risk and protective factors contributed to the development of SI over 7 years in

this high-risk subpopulation. Importantly, 27.1% of veterans with PTSD and/or MDD who did not endorse SI at baseline developed SI during the course of 7 years of the study. Lower levels of purpose in life, conscientiousness, and frequency of religious service attendance were most strongly associated with developing SI. These findings help to characterize potential targets for population-based prevention and treatment efforts that may help mitigate suicidality in high-risk veterans.

## Combat-Related Moral Injury and Suicidality

Another military-related stressor that has been associated with elevated risk for suicide is moral injury. Moral injury is defined as "the psychological, biological, spiritual, behavioral, and social impact of perpetrating, failing to prevent, or bearing witness to acts that transgress deeply held moral beliefs and expectations" [(47), p. 698], and often includes feelings of guilt and shame (47). Moral injury can occur by transgressions by self (e.g., killing a child), transgressions by others (e.g., witnessing torture committed by others), and betrayal experiences (e.g., perceived failures by leadership or fellow service members). Using NHRVS data, Wisco et al. (42) found that 10.8–25.5% of U.S. combat veterans reported being exposed to potentially morally injurious experiences. In particular, transgressions by self were found to be associated with current mental disorders and SI, and betrayal with post-deployment suicide attempts, even after adjustment for severity of combat exposure. Building upon this work, Corona et al. (44) investigated whether global purpose and meaning in life moderated the relationship between potentially morally injurious experiences and SI in combat veterans. Results revealed that greater global purpose and meaning in life was associated with significantly lower likelihood of experiencing SI among veterans who reported higher levels of transgression by others and betrayal experiences.

## Military Sexual Trauma and Suicidality

Effectively responding to suicide risk among veterans involves further understanding reactions to military-related stressors, including military sexual trauma (MST). Veterans with a history of MST (i.e., sexual assault and/or sexual harassment during service) are at elevated risk for suicide. Accordingly, Monteith et al. (43) sought to identify psychiatric and interpersonal correlates of suicidal ideation and suicide attempt among NHRVS veterans with a history of MST. The study found MST survivors who reported more severe alcohol use problems and perceived general disapproval from others in relation to their worst traumatic event were significantly more likely to report current SI and a lifetime suicide attempt; psychological distress was additionally linked to current SI.

## Clinical Implications

Collectively, results of NHRVS studies on suicidality conducted to date indicate that a considerable proportion of U.S. veterans experience SI, and that SI courses may fluctuate over time. These findings underscore the importance of periodic monitoring of suicidal thoughts and behaviors in this population (40). Further, prevention and treatment efforts designed to mitigate psychiatric and physical health comorbidities, loneliness, and disability in instrumental activities of daily living, and bolster social connectedness (i.e., secure attachment style and perceived social support) and protective psychosocial characteristics (i.e., curiosity, resilience, acceptance-based coping) may help mitigate risk for SI in veterans (40, 41). In high-risk veterans with comorbid PTSD/MDD, higher levels of purpose in life, curiosity, conscientiousness, and optimism were associated with decreased risk of SI (45, 46). Finally, results of these studies highlight the important of routine assessment of MST and potentially morally injurious experiences in the assessment, monitoring, and treatment of suicidality in veterans.

# AGING

More than half (65%) of veterans are currently aged 55 or older (48) and it is projected that this proportion of aged veterans will increase over the next two decades (49). There is an new focus potentially modifiable protective psychosocial characteristics in veterans, such as resilience, optimism, and religiosity, which may help older persons adapt to negative life events such as medical and psychiatric illness and promote successful aging (50). To date, twelve studies (see **Table 3**) focusing on aging-related topics have been published utilizing NHRVS data. The majority of these studies have examined characteristics that may help promote successful aging in veterans.

## Successful Aging

Using data from C1 of the NHRVS, Pietrzak et al. (56) found that the majority (82%) of 60–96 year old veterans rated themselves as aging successfully, and that physical and mental health difficulties were most strongly negatively related to successful aging. Additionally, after adjustment for these risk factors, resilience, gratitude, purpose in life, and community integration were strongly positively related to successful aging. Subsequently, Rozanova et al. (58) qualitatively evaluated veterans' perceptions of factors important to successful aging. Results of this study resonated with those of the quantitative study, suggesting that older veterans emphasize health behaviors, social engagement, and dispositional characteristics as key determinants of successful aging.

## Purpose in Life and Physical Disability

Physical disability is an important aspect of aging that may negatively affect functioning and quality of life in older veterans. Accordingly, elucidation of modifiable factors that may help buffer against the development of physical disability are critical to further understanding determinants of successful aging. Mota et al. (59) found that over 2 years, the incidence of new-onset physical disability among veterans aged 55 years and older was 11.5%. Importantly, purpose in life, which may be modified using adjunctive intervention strategies such as logotherapy, was found to be protective against the development of physical disability. Retirement, which may lead to a reduced sense of purpose and meaning in life, was found to be a risk factor for this outcome.

**TABLE 3 |** Aging.

| Citation | Title | Sample | Findings | Clinical implications |
|---|---|---|---|---|
| Fanning and Pietrzak (51) | Suicidality among older male veterans in the United States: Results from the National Health and Resilience in Veterans Study | Cohort 1 ($n = 1,962$) | Six percent of veterans reported past 2-week suicidal ideation, and combat veterans were more likely to contemplate suicide than non-combat veterans. | The low rate of treatment among veterans contemplating suicide underscores the need to improve outreach to at-risk older veterans in the general veteran population. |
| Pietrzak and Cook (52) | Psychological resilience in older U.S. veterans: Results from the National Health and Resilience in Veterans Study | Cohort 1 ($n = 2,025$) | Among older U.S. veterans who endured a high number of traumas in their lifetimes, nearly 70% were psychologically resilient in later life. | Lack of disability, secure attachment style, college/higher education, emotional stability, community integration, and purpose in life were strongly related to resilience. Population-based interventions targeting modifiable factors such as community integration and purpose in life may help promote resilience in veterans. |
| Kuwert et al. (53) | Loneliness among older veterans in the United States: Results from the National Health and Resilience in Veterans Study | Cohort 1 ($n = 2,025$) | 44% of veterans reported feeling lonely at least some of the time. The largest magnitude associations were observed for support and secure attachment style negatively associated with loneliness, and depressive symptoms being positively associated. | Results underscore the importance of multifactorial approaches (such as health and psychosocial approaches) in the prevention and treatment of loneliness in older veterans. |
| Levy et al. (54) | Lower prevalence of psychiatric conditions when negative age stereotypes are resisted | Cohort 1 ($n = 2,031$) | The prevalence suicidal ideation, anxiety, PTSD was found to be significantly lower among participants who fully resisted negative age stereotypes, compared to those who fully accepted them. | Findings underscore the importance of taking negative age stereotypes into account in etiological models of late-life psychiatric conditions. |
| Monin et al. (55) | From serving in the military to serving loved ones: Unique experiences of older veteran caregivers | Cohort 1 ($n = 2,025$) | Among the 20.4% of veteran caregivers, combat exposure was associated with less emotional caregiving strain and grandparenting was associated with increased perception of caregiving reward. Gratitude, happiness, and social support were additionally associated with greater reward. | Results suggest that significant early-life stressors may help confer greater resilience to the emotional demands of caregiving in older age and that both the caregiving context (i.e., hours, relationship type) and caregivers' attitudes may contribute to strain and reward. |
| Pietrzak et al. (56) | Successful aging among older veterans in the United States | Cohort 1 ($n = 2,025$) | Most older veterans rated themselves as aging successfully. Physical health difficulties and current psychological distress were most strongly negatively related to successful aging, while resilience, gratitude, and purpose in life, were most strongly positively related. | A dimensional approach to studying successful aging may help inform the development of clinical assessment, prevention, and treatment strategies that go beyond symptom management and work toward promoting functioning and well-being in older veterans. |
| Blais et al. (57) | Barriers and facilitators related to mental health care use among older veterans in the United States | Cohort 1 ($n = 2,025$) | Current utilization was associated with lifetime PTSD or depression, lifetime drug use disorder, severity of current psychiatric symptoms, medical difficulties, and lower perceptions of stigma. | Results highlight the importance of efforts to identify veterans who may benefit from mental health care because of predisposing and need characteristics, such as mental and physical health disorders. |
| Rozanova et al. (58) | Perceptions of determinants of successful aging among older U.S. veterans: results from the National Health and Resilience in Veterans Study | Cohort 1 ($n = 2,025$) | Older U.S. veterans emphasized health behaviors, social engagement, and dispositional characteristics as key determinants of successful physical, emotional, and cognitive aging | Older veterans emphasize individual health behaviors, self-reliance, and social connectedness as key determinants of successful aging. Prevention efforts to promote these factors may help promote successful aging |
| Mota et al. (59) | Purpose in life is associated with a reduced risk of incident physical disability in aging U.S. military veterans | Cohort 1 Baseline and Wave 2 ($n = 1,686$) | Older age, being married/cohabiting, retirement, and number of medical conditions were associated with an increased risk of any incident disability. Purpose in life was found to be protective for incident disability. | Purpose in life may help mitigate risk of physical disability through a broad range of mechanisms. Further research should evaluate whether interventions to increase purpose in life may help mitigate risk for physical disability among older veterans. |
| Weiner et al. (60) | Age differences in the association of social support and mental health in male U.S. veterans: Results From the National Health and Resilience in Veterans Study | Cohort 1 ($n = 619$) | Higher perceived support was associated with fewer mental health difficulties in younger but not older veterans, while community integration was associated with fewer mental health difficulties in older but not younger veterans. | Interventions targeting general mental health or global distress in younger male veterans should focus on enhancement of close relationships and feelings of support; whereas interventions focused on older male veterans should encourage integration in the community. |
| Monin et al. (61) | Older age associated with mental health resiliency in sexual minority US veterans | Cohort 1 ($n = 3,095$) | Younger LGB veterans were most likely to report lifetime depression and/or PTSD and current depression compared with heterosexual and older LGB veterans. Older LGB veterans had low levels of mental health problems, but reported the smallest social support networks. | Engaging older LGB veterans as a social support resource (e.g., mentoring) to help improve and/or protect the mental health of younger LGB veterans may also have positive effects for the older LGB mentors by increasing their social resources. |
| Levy et al. (62) | Active coping shields against negative aging self-stereotypes contributing to psychiatric conditions | Cohort 1 Baseline, Wave 2, and Wave 3 ($n = 3,157$) | Veterans with more negative age stereotypes were more likely to develop psychiatric conditions. Active coping decreased the likelihood of older individuals experiencing a detrimental health impact from negative age stereotypes. | Active coping may help blunt the adverse impact of negative age stereotypes, thus suggesting that efforts to promote adaptive coping skills may help mitigate risk for psychiatric conditions in older veterans. |

## Caregiving in Veterans

Employment may play a role in fostering a greater sense of purpose in life, and with the aging veteran population reaching retirement age, understanding the roles that veterans maintain later in life could be a useful mechanism for promoting successful aging. Indeed, older veterans may transition to providing care to their family members as they reach retirement or face other challenges, as it is estimated that one in 10 of all caregivers in the U.S. have served in the military (63). Monin et al. (55) found that greater perceived resilience was negatively associated with veteran caregiver physical strain. Depressive symptoms were positively associated with emotional strain (55). Additionally, gratitude, happiness, and social support were associated with greater perceived rewards related to caregiving (55).

## Social Connectedness and Psychological Resilience

Social connectedness recurrently appears as an important factor in successful aging and resilience among older veterans who participated in the NHRVS. Fanning and Pietrzak (51) found that social connectedness was negatively related to SI in older veterans. Weiner et al. (60) investigated the effects of different types of social engagement in older veterans, and found that community integration, but not perceived social support, was associated with fewer mental health difficulties in older veterans. In a study of sexual minority veterans [i.e., lesbian, gay, bisexual; Monin et al. (61)] found that, relative to younger veterans, older veterans had lower levels of mental health problems, but they reported the smallest social support networks. Finally, Kuwert et al. (53) found that 44.0% of veterans reporting feeling lonely at least some of the time, with 10.4% reporting often feeling lonely. While depressive symptoms were strongly related to loneliness in this study, greater, perceived social support and having a attachment style were negatively related to this outcome.

## Psychological Resilience in Late-Life

Significant changes and losses are common in older adulthood and include retirement, erosion of social networks, and reductions in functioning and mobility. It has been proposed that experiencing trauma and stressors before late adulthood may "inoculate" and help enhance coping skills in older adults (52, 64). It has been hypothesized that experiencing trauma or stressors earlier in life may promote psychological resilience to future traumas and stressors (52, 64). Using data from the NHRVS, Pietrzak and Cook (52) found that among older veterans who endured a high number of traumas in their lifetimes, nearly 70% were psychologically resilient in later life. Relative to distressed veterans, resilient veterans were younger, more likely to be White, less likely to have physical health difficulties and psychiatric histories. Resilient veterans also endorsed higher levels of emotional stability, prosocial behaviors (e.g., altruism), gratitude, purpose in life, and lower levels of openness to experiences (52). These findings suggest that prevention and treatment efforts designed to enhance gratitude, sense of purpose, and altruism may help promote resilience in trauma-exposed veterans.

Negative age stereotypes, defined as deprecating beliefs about older people as a category, have been linked to a broad range of negative health outcomes, including cardiovascular disease, cognitive decline, and mortality (65). Using NHRVS data, Levy et al. (54) evaluated whether negative age stereotypes may also be linked to risk for mental disorders in older veterans who participated in the NHRVS. They found that the prevalence of SI (5.0 vs. 30.1%), anxiety (3.6 vs. 34.9%), and PTSD (2.0 vs. 18.5%) was significantly lower among older veterans who fully resisted negative age stereotypes, compared to those who fully accepted them. A 4-year prospective cohort study of this cohort further revealed that greater resistance of negative age stereotypes was linked to significantly lower incidence of these outcomes and that engagement in active coping moderated this association (62); specifically, among veterans with more negative age stereotypes, those who engaged in active coping strategies to manage stress were less likely to develop mental health problems relative to those who did not engage in these strategies. Collectively, these results suggest that strategies to promote positive age stereotypes (66) and engagement in active coping may help mitigate risk for mental illness in older veterans.

## Barriers to Mental Healthcare

Between 41 and 79% of older persons with psychiatric disorders do not receive mental health care (67, 68). Perceived barriers to care, including stigma, negative beliefs about mental health care, and logistical barriers to care, may also affect utilization of mental health services among older veterans (57). Blais et al. (57) analyzed NHRVS data to identify correlates of current mental health care utilization and perceived barriers to care in older veterans. Only 6% of older veterans reported current mental health care utilization, and among veterans who screened positive for a current psychiatric disorder 25% were currently utilizing services. Utilization was also associated with several medical and psychiatric disorders, most notably PTSD (odds ratio = 5.9). Notably, greater perceptions of stigma and negative beliefs about mental health care were related to decreased likelihood of utilizing care. Collectively, these results suggest that efforts to identify veterans with mental health distress, and to reduce stigma and negative beliefs about mental health care may help promote mental health service utilization among symptomatic older U.S. veterans.

## Clinical Implications

A majority of veterans with a high lifetime trauma burden are psychologically resilient in later life (52). However, a significant minority of older veterans may experience a clinically significant exacerbation of PTSD symptoms in late life (12). Prevention and treatment efforts designed to promote health behaviors, protective psychosocial characteristics (i.e., resilience, gratitude, purpose in life), social connectedness (i.e., secure attachment, community integration, social engagement), and cognitive functioning may help promote successful aging in older veterans and mitigate risk for mental disorders (12, 51–53, 56, 58, 60). Further, since physical disability is prevalent among older veterans, promoting a greater sense of purpose in life may help preserve physical functioning in aging veterans (59). Efforts to identify distressed older veterans and reduce stigma and negative beliefs about mental health care may help increase mental

health service utilization (57). In sum, results of these studies suggest that interventions designed to mitigate psychological and physical struggles in older veterans, and to promote social connectedness and protective psychosocial characteristics, may help foster successful aging in veterans.

## SPECIAL TOPICS RELEVANT TO VETERANS

Twenty-five (see **Table 4**) studies from the NHRVS have examined a myriad of special topics relevant to veterans, including military sexual trauma, combat exposure, positive and negative effects of military service, homelessness, and psychiatric and physical morbidities/comorbidities.

### Military Sexual Trauma and Combat Exposure

Certain trauma exposures are unique to veterans, including military sexual trauma and combat exposure. While the prevalence of MST is highest in female veterans, the VA reports that almost half of VA users who screen positive for MST are men (93). Furthermore, MST is also thought to be largely underreported, particularly in men, among whom there may be a higher burden of stigma. Using NHRVS data, Klingensmith et al. (69) found that 7.6% of U.S. military veterans reported MST, and that the prevalence was significantly higher among female than male veterans (32.4 vs. 4.8%) and younger than older veterans (22.8% among 18–29 year-olds vs. 4.5% among 60+ year-olds). In a model adjusted for sociodemographic and military characteristics, MST was associated with elevated rates of several psychiatric morbidities and suicidality (adjusted odds ratio range = 2.2–3.1), reduced functioning and QOL, as well as increased mental health treatment utilization (adjusted odds ratios range = 2.4–3.7) (69). A follow-up study by Averill et al. (86) found that, relative to female MST survivors, male MST survivors have greater trauma burden, hostility, and higher rates of drug use disorder, but lower severity of PTSD symptoms. Taken together, these findings suggest that screening for MST and the consideration of sex differences are critical to informing risk for a broad range of mental health problems in U.S. veterans.

Similar to MST, combat exposure is linked to increased risk for mental health problems, including psychiatric disorders such as PTSD, generalized anxiety disorder, MDD, and substance use (94, 95). A NHRVS study (76) found 38% of veterans reported being exposed to combat, and that, relative to non-combat veterans, combat veterans had 2 to 3-fold elevated rates of PTSD and generalized anxiety disorder. Further, combat veterans had 68% greater odds of a suicide attempt and 85% and 38% greater odds of a stroke and chronic pain, respectively. Among combat veterans, age was associated with differential risk for certain health conditions, with younger veterans more likely to screen positive for PTSD, SI, and migraine headaches, while older veterans were more likely to reported having heart disease and a heart attack. Results of this study suggest that combat exposure may independently contribute to risk for mental and physical health issues in U.S. veterans, and that age may moderate the effect of combat exposure on health outcomes.

### Perceived Effects of Military Service

In addition to combat exposure, other military-related factors, such as perceived threat during deployment, and difficult living and working environments, have been linked to depression, anxiety, and PTSD (96). Using NHRVS data, Campbell et al. (78) examined the relationship between perceptions of desirable (e.g., military service helped one learn to cope with adversity) and undesirable effects of service (e.g., military service caused misery and discomfort), and mental health problems. The study found desirable effects of service were more frequently endorsed than undesirable effects (54–86% vs. 9–48%), and that combat-exposed veterans were more likely to endorse undesirable than desirable effects of service (11–60% vs. 4–41%). Of note, after adjustment for possible confounding variables, undesirable effects of service predicted significantly greater odds of probable current mental health disorders and current SI (both odds ratios = 1.1), while desirable effects of military service were linked to lower odds of current SI (odds ratio = 0.96). Taken together, results of this study suggest that perceptions of military service may be linked to risk for mental disorders and suicidality, and that desirable effects of effects of military service may help counteract risk for suicidal thinking associated with undesirable effects of service. Clinically, they suggest that assessment of perceptions of military service may help identify at-risk veterans who may benefit from mental health treatment.

### Major Depressive Disorder

MDD is prevalent disorder that often co-occurs with PTSD. Using data from the NHRVS, Nichter et al. (84) estimated the prevalence of current PTSD/MDD in the U.S. veterans population at 3.4%. Compared to veterans with PTSD only and MDD only, those with comorbid PTSD/MDD were significantly more likely to screen positive for current SI, lifetime suicide attempts, and anxiety disorders, and they scored substantially lower on measures of mental health and cognitive functioning, and QOL. Furthermore, a follow-up study (85) found that veterans with comorbid PTSD/MDD had a substantially greater burden of physical illness than veterans with either disorder alone. Specifically, veterans with comorbid PTSD/MDD had higher rates of heart disease, migraine, fibromyalgia, and rheumatoid arthritis compared to veterans with MDD alone, and higher rates of hypercholesterolemia and hypertension compare to veterans with PTSD alone (85). Taken together, these findings highlight the importance of screening, monitoring, and treatment comorbid PTSD/MDD in veterans. They also suggest that veterans with comorbid PTSD/MDD should be closely monitored for physical health problems, particularly cardiovascular risk factors and disease, and inflammatory and pain-related conditions. Finally, emerging NHRVS research on PTSD/MDD comorbidity (89) has revealed that greater dispositional optimism and community integration were associated with lower likelihood of having comorbid PTSD/MDD relative to either disorder alone, thus highlighting

**TABLE 4 |** Special topics relevant to veterans.

| Citation | Title | Sample | Findings | Clinical implications |
|---|---|---|---|---|
| Klingensmith et al. (69) | Military sexual trauma in US veterans: Results from the National Health and Resilience in Veterans Study | Cohort 2 ($n$ = 1,468) | Almost 8% of US veterans screened positive for MST, with higher rates among female and younger veterans. MST was associated with elevated rates of comorbidities and suicidality, reduced functioning and quality of life. | Screening for MST may help identify veterans who are at risk for a broad range of mental health and functional difficulties, as well as increased need for mental health services. |
| Tsai et al. (70) | U.S. female veterans who do and do not rely on VA Health care: Needs and barriers to mental health treatment | Cohort 1 and Cohort 2 ($n$ = 1,202) | Female VA patients were more likely to be low income, not employed, from racial-ethnic minority groups, combat veterans, and were more likely to have a disability, screen positive for PTSD, and report poorer mental health-related functioning than non-VA female veterans. | VA may serve as a health care "safety net" for many female veterans; female and male veterans experience similar stigma-related barriers to mental health care, such as fear of being perceived as weak. |
| Fuehrlein et al. (71) | The burden of alcohol use disorders in US military veterans: Results from the National Health and Resilience in Veterans Study | Cohort 1 ($n$ = 3,157) | Younger age, male sex, lower education, lower income and greater number of life-time traumatic events were associated with life-time AUD. | Comprehensive assessment of trauma histories, as well as monitoring and treatment of trauma-related psychopathology and suicidality, may help mitigate risk for AUD in veterans. |
| Sippel et al. (72) | The burden of hostility in U.S. veterans: Results from the National Health and Resilience in Veterans Study | Cohort 1 Baseline and Wave 2 ($n$ = 2,157) | Protective psychosocial characteristics and aspects of social connectedness were negatively associated with hostility. Psychological distress predicted all symptomatic hostility courses, while alcohol misuse predicted chronic aggressive urges and all symptomatic courses of difficulties controlling anger. | Aggressive urges and difficulties controlling anger are prevalent in U.S. veterans. Integrated treatments that target psychological distress and alcohol use problems, and bolster protective psychosocial factors and social connectedness may be helpful in mitigating hostility and anger in veterans. |
| Tsai et al. (73) | Homelessness among a nationally representative sample of US veterans: Prevalence, service utilization, and correlates | Cohort 1 Wave 3 ($n$ = 1,533) | Among all veterans, 8.5% reported any lifetime homelessness in their adult life, but only 17.2% of those reported using VA homeless or social services. | Veterans with low income, and poor mental and physical health, were more likely to have experienced homelessness and may most benefit from targeted services. There may also be barriers to care for many homeless veterans, especially for those who live in rural areas. |
| Heinz et al. (74) | American military veteran entrepreneurs: A comprehensive profile of demographic, service history, and psychosocial characteristics | Cohort 1 ($n$ = 1,285) | Self-employed veterans were more likely to serve in Vietnam and to serve in the military for fewer years. Higher levels of openness, extraversion, optimism, purpose in life, and greater need for autonomy and professional development were observed among self-employed veterans. | Results highlights the significant scope of job creation and economic activity driven by self-employed veterans; they also highlight the psychosocial profile of this population. |
| Stefanovics et al. (75) | Gambling in a national U.S. veteran population: Prevalence, sociodemographics, and psychiatric comorbidities | Cohort 1 ($n$ = 3,157) | More than a third of U.S. veterans gamble recreationally, with a 2.2% screening positive for problem gambling. Both recreational and problem gambling were associated with elevated trauma burden and psychiatric comorbidities. | Findings underscore the potential utility of screening and treatment initiatives for gambling among veterans, and of the importance of trauma as a risk factor for problem gambling in veterans. |
| Thomas et al. (76) | Mental and physical health conditions in US combat veterans: Results from the National Health and Resilience in Veterans Study | Cohort 2 ($n$ = 1,480) | Compared to non-combat veterans in the United States, combat veterans have elevated rates of PTSD, suicide attempt, stroke, and chronic pain independent of other sociodemographic, military, and mental health factors. | Identifying, screening, and treating combat veterans, and promoting access to and use of integrated mental and physical health services is extremely important, as combat veterans potentially face complex mental and physical health symptoms after deployment. |
| Ziobrowski et al. (77) | Gender differences in mental and physical health conditions in U.S. veterans: Results from the National Health and Resilience in Veterans Study | Cohort 1 ($n$ = 3,157) | Female veterans had higher prevalence estimates of lifetime and current psychiatric conditions, and lifetime histories of arthritis, migraine headaches, and osteoporosis, but lower prevalence estimates of lifetime substance use disorders, and lifetime histories of diabetes, heart attack, and high blood pressure. | There are substantial gender differences in the prevalence of many health conditions in veterans. With more women joining the military, consideration of their unique health needs is critical for delivering gender-sensitive care and developing effective health interventions. |
| Campbell et al. (78) | Association between perceptions of military service and mental health problems in a nationally representative sample of United States military veterans | Cohort 2 ($n$ = 1,484) | Desirable effects of service were more frequently endorsed than undesirable effects, but perceptions of military service were associated with suicidal ideation and other mental health conditions. | Findings underscore the importance of evaluating veterans' perceptions of service in therapy. Assessing perceptions of service could also be used as a method to identify possible at-risk veterans who might benefit from mental health services and resources. |

*(Continued)*

**TABLE 4 |** Continued

| Citation | Title | Sample | Findings | Clinical implications |
|---|---|---|---|---|
| Fuehrlein et al. (79) | Trajectories of alcohol consumption in U.S. military veterans: Results from the National Health and Resilience in Veterans Study | Cohort 1 Baseline, Wave 2, and Wave 3 ($n = 3,150$) | Lifetime major depressive disorder was linked to an excessive drinking trajectory, while fewer medical conditions and lower social support were linked to a moderate drinking trajectory. Having a secure attachment style and greater social support, and absence of lifetime MDD was linked to recovery from excessive drinking. | Targeting depression and related interpersonal factors such as attachment style and social support in population-based prevention and treatment initiatives may help prevent, mitigate, and promote recovery from excessive alcohol consumption in veterans. |
| Norman et al. (80) | The burden of co-occurring alcohol use disorder and PTSD in U.S. military veterans: Comorbidities, functioning, and suicidality | Cohort 1 ($n = 3,157$) | Veterans with AUD/PTSD were more likely to screen positive for depression, anxiety, suicidal ideation, to have attempted suicide. They also scored lower on measures of functioning and quality of life. | Findings highlight the clinical severity, including both mental and physical health burden, associated with having PTSD in addition to AUD and the importance of screening veterans for these disorders. |
| Stefanovics et al. (81) | The physical and mental health burden of obesity in U.S. veterans: Results from the National Health and Resilience in Veterans Study | Cohort 1 ($n = 3,122$) | Obesity was associated with greater trauma burden; elevated rates of a broad range of physical and mental health conditions, poor quality of life, and decreased engagement in an active lifestyle. | Results underscore the importance of multicomponent behavioral interventions and weight management interventions, and consideration of the role of trauma and PTSD as risk factors for obesity in veterans. |
| El-Gabalawy et al. (82) | Physical health conditions associated with full and subthreshold PTSD in U.S. military veterans: Results from the National Health and Resilience in Veterans Study | Cohort 1 ($n = 3,157$) | Both full and subthreshold PTSD were associated with increased odds of sleep disorder and respiratory conditions. Full PTSD was associated with increased odds of osteoporosis or osteopenia and migraine, while subthreshold PTSD only was associated with increased odds of diabetes. | Dysphoric arousal symptoms of PTSD are particularly strongly linked to physical conditions. Sleep disturbances, in particular, may drive the relationship between PTSD symptoms, and respiratory and inflammatory diseases, and may be targeted in integrated mental-physical health interventions. |
| Straus et al. (83) | Differences in protective factors among U.S. Veterans with post-traumatic stress disorder, alcohol use disorder, and their comorbidity: Results from the National Health and Resilience in Veterans Study | Cohort 1 ($n = 3,157$) | Comorbid PTSD/AUD had lower social/psychosocial protective factors than AUD-only. Social/psychosocial factors partially mediated PTSD and suicidal ideation. Only psychosocial factors partially mediated link between PTSD and suicide attempts. | Enhancing protective factors within psychological treatments, such as strength-based interventions that aim to foster pre-existing protective factors, may contribute to better clinical outcomes in veterans with PTSD and AUD. |
| Meffert et al. (2) | US veterans who do and do not utilize veterans affairs health care services: Demographic, military, medical, and psychosocial characteristics | Cohort 1 ($n = 3,152$) | Veterans who use VA services have a substantially elevated mental and physical health burden compared to other veterans. The primary factor differentiating VA users from those that did not was presence of lifetime psychopathology. | Results highlight the importance of specialty VA services targeting PTSD, depression, anxiety, social phobia, DUD, and suicidality. Education efforts targeting cultural and/or social norms that interfere with help-seeking behavior in veterans may also help connect veterans to care. |
| Nichter et al. (84) | Psychological burden of PTSD, depression, and their comorbidity in the U.S. veteran population: Suicidality, functioning, and service utilization | Cohort 1 ($n = 2,732$) | Veterans with probable PTSD/MDD were more likely to have attempted suicide and scored lower on measures of functioning and quality of life and screen positive for current suicidal ideation, lifetime suicide attempts, probable generalized anxiety and social anxiety disorders. | Results suggest that the deleterious effects of PTSD and MDD on mental health functioning and QoL are additive, such that their co-occurrence is associated with the largest magnitude of impairment relative to each disorder alone. |
| Nichter et al. (85) | Physical health burden of PTSD, depression, and their comorbidity in the U.S. veteran population: Morbidity, functioning, and disability | Cohort 1 ($n = 2,732$) | Veterans with comorbid PTSD/MDD were more likely to be diagnosed with heart disease, migraine, fibromyalgia, and rheumatoid arthritis compared to those with MDD-only, and were at greater odds of being diagnosed with hypercholesterolemia and hypertension relative to those with PTSD-only. | Veterans with co-occurring PTSD/MDD may be at increased risk for the development of cardiovascular disease. Results suggest the importance of integrating mental health services in primary care settings to increase access and utilization among older veterans. |
| Averill et al. (86) | Sex differences in correlates of risk and resilience associated with military sexual trauma | Cohort 2 ($n = 115$) | Compared to female MST survivors, male MST survivors reported increased lifetime traumatic events, hostility, and history of drug use disorder, whereas female veterans reported increased lifetime PTSD symptoms. | Results suggest that there may be gender-specific clinical profiles in veterans who experienced MST, which may help inform personalized interventions in this population. |

*(Continued)*

**TABLE 4 |** Continued

| Citation | Title | Sample | Findings | Clinical implications |
|---|---|---|---|---|
| Baldassarri et al. (87) | Nicotine dependence in US military veterans: Results from the National Health and Resilience in Veterans Study | Cohort 1 ($n = 3,157$) | 19.4% of veterans met criteria for lifetime nicotine dependence. Veterans with lifetime nicotine dependence were more likely to have psychiatric and medical conditions and lower physical functioning compared with veterans without. | Veterans with lifetime nicotine dependence may require a comprehensive and integrated approach to mental and physical health care, which includes attention to mental and physical health comorbidities. |
| Carr et al. (88) | Race, ethnicity, and clinical features of alcohol use disorder among US military veterans: Results from the National Health and Resilience in Veterans Study | Cohort 1 ($n = 1,212$) | Black and Hispanic veterans with lifetime AUD may experience a higher disease burden relative to white veterans. | Results suggest higher disease burden for racial/ethnic minority veterans with AUD and underscore the importance of race/ethnicity-sensitive assessment, monitoring, and treatment of AUD for veterans. |
| Nitcher et al. (89) | Risk and protective factors associated with comorbid PTSD and depression in U.S. military veterans: Results from the National Health and Resilience in Veterans Study | Cohort 1 ($n = 2,732$) | Racial/ethnic minority status, number of lifetime traumas, and time spent engaged in private religious/spiritual activities were associated with PTSD/MDD status, while higher scores on measures of community integration and dispositional optimism were negatively associated with comorbid PTSD/MDD status. | Results underscore the need to study whether targeting dispositional optimism and community integration in prevention and treatment efforts for PTSD/MDD may enhance clinical outcomes in this difficult-to-treat population. |
| Straus et al. (90) | Determinants of new-onset alcohol use disorder in U.S. military veterans: Results from the National Health and Resilience in Veterans Study | Cohort 1 Baseline, Wave 2, Wave 3, and Wave 4 ($n = 1,770$) | Approximately 6% of veterans developed AUD over 7-year follow-up period. Drug disorders, alcohol use, and trauma characteristics were associated with risk of developing AUD. | Results underscore the importance of prior substance use history, as well as trauma-related factors such as adult sexual trauma and anxious arousal symptoms, as determinants of incident AUD. |
| Stefanovics et al. (91) | PTSD and obesity in U.S. military veterans: Prevalence, health burden, and suicidality. | Cohort 1 ($n = 3,157$) | 5.8% of U.S. veterans have co-occurring PTSD and obesity. Veterans with PTSD and obesity have elevated mental and physical health burden and suicide risk. | Integrated, multi-component interventions targeting PTSD and comorbid obesity may help mitigate the elevated mental and physical health burden in this population. |
| Stefanovics et al. (92) | Smoking, obesity, and their co-occurrence in the U.S. military veterans: Results from the National Health and Resilience in Veterans Study | Cohort 1 ($n = 3,157$) | The prevalence of co-occurring obesity and smoking among U.S. veterans was 5.4%. Co-occurring obesity and smoking was positively associated with mental and physical health problems, higher level of trauma and stress burden, and lower quality of life. | Findings underscore the importance of multi-component interventions targeting obesity and smoking in veterans. |

the potential importance of targeting these psychosocial factors in prevention and treatment efforts.

## Alcohol Use Disorder

Although PTSD is one of the most prevalent and intensively studied psychiatric disorders among veterans, other disorders are also prevalent among veterans. With regard to alcohol use disorder (AUD), Fuehrlein et al. (71) found the lifetime and past-year prevalence of AUD was 42.2 and 14.8%, respectively in the NHRVS. Results further revealed that veterans with lifetime AUD were approximately four times more likely to have a lifetime history of PTSD, MDD, and SI (78). When considering racial/ethnic differences in veterans associated with AUD, a recent study found that Black and Hispanic veterans with lifetime AUD experience a greater disease burden relative to White veterans, which underscores the importance of race/ethnicity-sensitive approaches to the assessment, monitoring, and treatment of AUD in veterans (88).

Building on these cross-sectional findings of AUD in veterans, a 4-year prospective cohort study (79) was conducted to identify predominant trajectories of alcohol consumption and baseline determinants of these trajectories, where four predominant trajectories were identified. The majority (65.3%) of veterans were rare drinkers, 30.2% were moderate drinkers, 2.6% were excessive drinkers (2.6%), and 1.9% were recovering drinkers. Lifetime MDD was linked to an excessive drinking trajectory, while fewer medical conditions and lower social support were linked to a moderate drinking trajectory. Absence of lifetime MDD, having a secure attachment style, and greater social support were linked to the recovering drinking trajectory (84). Another prospective study (90) found that ∼6% of veterans without AUD at baseline developed AUD over 7-year follow-up. Adult sexual trauma in adulthood, higher anxious arousal symptoms of PTSD, lifetime history of drug and nicotine use disorders, and higher alcohol consumption at baseline predicted the development of AUD. Collectively, these results suggest that targeting MDD, other substance use, and trauma exposure in population-based prevention and treatment initiatives may help prevent, mitigate, and promote recovery from AUD in veterans.

Given that AUD and PTSD are among the most prevalent disorders in veterans and often co-occur, it is important to determine the burden associated with AUD/PTSD comorbidity relative to either disorder alone. Using NHRVS data, Norman et al. (80) found that one of every five veterans with AUD

also screened positive for PTSD. Veterans with comorbid PTSD/AUD, comparted to AUD only veterans, were more likely to screen positive for MDD, GAD, and reported strikingly higher rates of current SI (39.1 vs. 7.0%) and lifetime suicide attempt(s) (46.0 vs. 4.1%); they also scored lower on measures of cognitive, mental, and physical health functioning, and QOL (80). Building on this study, Straus et al. (83) examined social (e.g., social connectedness) and psychosocial characteristics in veterans with PTSD, AUD, and comorbid PTSD/AUD. The study found veterans with comorbid PTSD/AUD had lower on social connectedness and protective psychosocial characteristics relative to those with AUD alone, but not PTSD alone. While both social and psychosocial protective factors partially mediated the relation between PTSD and current SI, only psychosocial protective characteristics partially mediated the relation between PTSD and lifetime suicide attempt(s) (83). Collectively, these findings highlight the burden of comorbid PTSD/AUD in veterans and suggest that treatment of PTSD in veterans with PTSD/AUD, and promotion of social connectedness and psychosocial protective factors, may help mitigate risk for and promote recovery from these disorders.

## Nicotine Dependence

Another commonly used substance in veterans is nicotine. Baldassarri et al. (87) found that almost one in five U.S. veterans met criteria for lifetime nicotine dependence. The strongest correlates of lifetime nicotine dependence were lifetime alcohol use disorder, lifetime drug use disorder, current alcohol use disorder, kidney disease, and heart disease. Given that nicotine dependence often presents as part of a complex set of conditions that includes psychiatric and medical comorbidities, trauma history, reduced overall physical functioning, and an increase in somatic complaints, veterans with nicotine dependence may require a comprehensive and integrated approach to care.

## Problem Gambling

PTSD has also been associated with problem gambling (97) and 40% of veterans seeking treatment for gambling problems have reported prior suicide attempts, with 64% of those who attempted suicide reported gambling-related attempts (98). Using NHRVS data, Stefanovics et al. (75) examined the prevalence, risk factors, and mental health correlates of recreational and problem gambling in U.S. veterans. They found 35.1% of U.S. veterans gambled recreationally and 2.2% screened positive for problem gambling. Younger age, self-identifying as Black and being retired were associated with increased likelihood of screening positive for problem gambling. Veterans with problem gambling also had higher rates of substance use, anxiety, depressive disorders, a history of physical trauma or sexual trauma, and greater lifetime trauma burden. Results of this study suggest that a significant minority of U.S. veterans screen positive for problem gambling, which is associated with greater mental health burden. They further suggest that routine screening and monitoring of gambling severity may help identify at-risk veterans, and that trauma burden may contribute to risk for problem gambling in this population.

## Physical Health Morbidities

The relationship between trauma, PTSD, and physical health has been well-documented (99). Given that the clinical presentation of PTSD is often heterogeneous, examining the relation between PTSD and subthreshold PTSD, and a range of physical conditions may elucidate potential mechanisms driving comorbidity with physical health conditions. Using data from the NHRVS, El-Gabalawy et al. (82) found that PTSD and subthreshold PTSD were associated with increased risk of sleep disorder and respiratory conditions. PTSD was additionally associated with increased risk of osteoporosis or osteopenia and migraine, while subthreshold PTSD was associated with increased odds of diabetes. Results also demonstrated the importance of dysphoric arousal symptoms of PTSD, which are characterized by sleep disturbance, concentration difficulties, and irritability and anger, in risk models of certain physical conditions in veterans with PTSD symptoms.

NHRVS investigators have also examined the prevalence and health burden of obesity in U.S. veterans. A recent study found that 32.7% of NHRVS veterans were obese, which is higher than previously reported estimates in the U.S. veteran population (81). The prevalence of obesity was particularly elevated among veterans who were younger, racial/ethnic minorities, and who utilized VA healthcare services as their main source of healthcare. Notably, obesity was associated with greater trauma burden, as well as elevated rates of a broad range of mental health conditions, including PTSD and nicotine dependence (81). Further NHRVS studies have revealed that 5.8% of veterans have co-occurring PTSD and obesity and 5.4% of veterans have co-occurring nicotine dependence and obesity (91, 92). Obesity was also associated with a range of physical health conditions, such as diabetes, arthritis, and heart disease, in addition to poor physical and mental health-related functioning and overall QOL (91). Collectively, these findings underscore the burden of obesity—independently and in combination with smoking and PTSD—on multiple aspects of health, functioning, and QOL in veterans.

## Gender Differences

Gender differences have also been reported among veterans for specific health conditions. Risk for exposure to various types of traumatic events differs by gender (6) and the association of trauma with adverse health outcomes may vary by traumatic event type (69). Thus, it is important to consider the possibility that assaultive trauma may be differentially associated with health outcomes in male and female veterans. A recent study (77) found that female veterans had significantly higher prevalence of lifetime PTSD, MDD, arthritis, migraine headaches, and osteoporosis, but lower prevalence estimates of lifetime nicotine dependence, drug use, diabetes, heart attack, and high blood pressure. With more women joining the military, consideration of their unique health needs is critical to informing care delivery models and developing gender-sensitive interventions (77).

## Hostility and Anger

Understanding the burden and clinical features of hostility and anger is particularly relevant to veterans given evidence of elevated rates of hostility-related health issues such as PTSD,

depression, and heart disease relative to non-veterans (100, 101). Using data from the NHRVS, Sippel et al. (72) examined the prevalence and longitudinal course of hostility over a 2-year period. They found that 61.2% of veterans reported experiencing difficulties controlling anger and that nearly a fourth reported having aggressive urges (72). Psychological distress and alcohol misuse were associated with symptomatic courses of hostility, while greater dispositional optimism and a secure attachment style were negatively associated with these courses (72). These findings underscore the burden of hostility and anger in the U.S. veterans, and suggest potential targets for prevention and treatment efforts designed to mitigate hostility and anger in this population.

### Homelessness

Studies from the NHRVS have also contributed to the literature on homelessness and employment, which may help inform allocation of governmental resources and services for veterans. A 2016 study by Tsai et al. (73) found that 8.5% of veterans reported ever being homeless in their adult life, but only 17.2% of those reported ever using VA homeless services. Findings further revealed that low income, being middle-aged (15, 18, 37–41, 45–47), and having poor mental and physical health were independently associated with lifetime homelessness. Additionally, veterans who were White or lived in rural areas were significantly less likely to have used ever VA homeless services.

### Self-Employment

Efforts to support self-employment may help mitigate unemployment among veterans. Results from Heinz et al. (74) demonstrated that veteran entrepreneurs experienced a higher number of traumas compared to non-entrepreneurs, but veterans entrepreneurs did not report higher levels of PTSD or other psychopathology. These results suggest that higher trait levels of optimism, extraversion, gratitude, curiosity (i.e., need for autonomy), and openness may contribute to resilience in veteran entrepreneurs. Combined with elevated sense of purpose in life, there trains may help these individuals be more "gritty" and pursue entrepreneurial employment.

### Clinical Implications

Veterans face a wide array of mental and physical health struggles, many of which commonly co-occur, and may result in functional difficulties, and chronicity and exacerbation of symptoms. Results of the NHRVS studies reviewed above help to characterize the population-based burden of a wide range of mental and physical health conditions that are prevalent among veterans, which may help inform outreach efforts, resource allocation, and program development within VA and non-VA settings to better serve this population. They also highlight the need for screening initiatives and specialty services targeting homelessness, employment, and PTSD and co-occurring health disorders. Specifically, veterans with histories of MST and combat-exposure, as well as common co-occurring physical and mental health conditions may have heightened need for screening, monitoring, and treatment efforts. Increasing access to information about mental health care, which may serve to decrease stigma, may also help veterans navigate barriers to initiation and engagement in care.

## RESILIENCE AND POST-TRAUMATIC GROWTH

Although most studies on trauma focus on psychopathology and other negative consequences, a new concentration in trauma literature is to characterize the prevalence and correlates of psychological resilience in veterans. Psychological resilience is defined as "the ability to adapt in the aftermath of trauma or extreme stress and maintain a high level of psychological functioning" (3). There are several personality and behavioral constructs associated with stress resilience, including hardiness, mental toughness, and grit (102). Though these constructs have nuanced differences, they represent the positive psychological traits that may help foster psychological resilience. Additionally, positive psychological changes, or PTG, can occur as a consequence of exposure to traumatic and stressful life events, and may include developing an increased appreciation of life, greater sense of personal strength, renewed appreciation for intimate relationships, and positive spiritual changes (103). Longitudinal studies of resilience and PTG can help elucidate the nature and determinants of heterogeneous courses of reactions to stressful or traumatic events and help inform strategies for promoting positive psychological changes in the face of adversity (104). To date, eight NHRVS studies (see **Table 5**) have focused on resilience and post-traumatic growth.

### Psychological Resilience

As described above, studies from the NHRVS have found that the majority of veterans with a large number of traumatic experiences are psychologically resilient in later life and that prosocial behaviors and purpose in life may help promote psychological resilience (52). Although many cross-sectional studies have examined the correlates of veteran resilience, scarce longitudinal studies have identified longitudinal determinants of resilience in this population. Longitudinal data are important, as they can help inform population-based treatment and prevention initiatives geared toward the promotion of psychological resilience in trauma-exposed individuals such as veterans.

Toward this end, Isaacs et al. (107) conducted a 2-year prospective cohort study and found that among veterans endured a high number of traumas over the course of their lifetimes, 67.7% reported minimal-to-no current psychological distress (i.e., current PTSD, depression, and anxiety symptoms). Baseline determinants of resilience included younger age, White race/ethnicity, better physical health, lower rates of psychiatric and substance use disorders, and greater levels of emotional stability, extraversion, purpose in life, dispositional gratitude, and altruism, and lower openness to experiences (107). Cross-sectionally, research using the NHRVS has also found high levels of religiosity/spirituality is associated with decreased risk for PTSD, MDD, alcohol use disorder, and SI (108). Importantly, higher levels of religiosity/spirituality were also strongly linked

**TABLE 5 |** Resilience and post-traumatic growth.

| Citation | Title | Sample | Findings | Clinical implications |
|---|---|---|---|---|
| Tsai et al. (105) | Post-traumatic growth among veterans in the USA: Results from the National Health and Resilience in Veterans Study | Cohort 1 ($n = 3,157$) | 50.1% of all veterans and 72.0% of veterans who screened positive for PTSD reported at least "moderate" PTG in relation to their worst traumatic event. A quadratic relationship was found to best explain the relationship between PTSD symptoms and PTG. | Greater social support, purpose in life and intrinsic religiosity were independently associated with PTG, suggesting that clinical interventions designed to promote these factors may help foster post-traumatic growth. |
| Tsai et al. (106) | What doesn't kill you makes you stronger: A national study of U.S. military veterans | Cohort 1 Baseline and Wave 2 ($n = 1,057$) | Greater scores on the Personal Strength domain of the PTG Inventory-Short Form at baseline was associated with reduced severity and incidence of PTSD at a 2-year follow-up. | Veterans who perceive greater gains in personal strength, perhaps as a result of developing greater coping skills in response to previous traumas, may be better able to cope with subsequent traumas. |
| Tsai et al. (104) | Longitudinal course of post-traumatic growth among U.S. military veterans: Results from the National Health and Resilience in Veterans Study | Cohort 1 Baseline and Wave 2 ($n = 1,838$) | Five courses of PTG were identified. More than half of veterans who reported at least "moderate" PTG maintained that level 2 years later. PTSD symptoms, medical conditions, purpose in life, altruism, gratitude, religiosity, and an active reading lifestyle predicted maintenance or increase in PTG. | Potentially reading and writing about the trauma may facilitate PTG in veterans with PTSD and physical health conditions may help reduce burdens from these disorders. |
| Isaacs et al. (107) | Psychological resilience in U.S. military veterans: A 2-year, nationally representative prospective cohort study | Cohort 1 Baseline and Wave 2 ($n = 2,157$) | Results suggest that the majority of trauma-exposed veterans (67.7%) are psychologically resilient. Higher levels of emotional stability, extraversion, gratitude, purpose in life, and altruism, and lower levels of openness to experiences predicted resilient status. | Purpose in life, gratitude, and altruism, are potentially modifiable, and thus suggest possible population-based targets for prevention and treatment efforts designed to bolster psychological resilience in veterans. |
| Sharma et al. (108) | Religion, spirituality, and mental health of U.S. military veterans: Results from the National Health and Resilience in Veterans Study | Cohort 1 ($n = 3,151$) | Higher levels of religion/spirituality were also strongly linked with increased dispositional gratitude, purpose in life, and post-traumatic growth. | Broader spiritual activities/practices, such as mindfulness, yoga, and breathing-based meditation may have beneficial effects in mitigating symptoms of PTSD, depression and anxiety. |
| Tsai and Pietrzak (109) | Trajectories of post-traumatic growth among US military veterans: A 4-year nationally representative, prospective cohort study | Cohort 1 Baseline, Wave 2, and Wave 3 ($n = 2,718$) | Greater severity of re-experiencing and avoidance PTSD symptoms at baseline predicted "Consistently Moderate" and "High and Increasing" PTG trajectories. Compared to the "Low and Decreasing" trajectory, the "High and Increasing PTG" trajectory scored higher on baseline measures of gratitude, purpose in life, spirituality, and social support. | Multidisciplinary approaches that include peer support programs, spiritual leaders, and loved ones in the clinical process may be needed to enhance these deep philosophical domains of life and functioning, and help facilitate PTG. |
| Martz et al. (110) | Post-traumatic growth moderates the effect of post-traumatic stress on quality of life in U.S. military veterans with life-threatening illness or injury | Cohort 1 ($n = 418$) | PTSD was inversely associated with quality of life. Both PTGI-Total and all five PTGI subscales successfully moderated the influence of PTSD on perceived quality of life. | Acceptance and Commitment Therapy or Coping Effectiveness Training may help individuals with life-threatening injuries and medical conditions with finding some positive aspects of life that can instill new meanings, despite the fact that their medical conditions may never be cured and could even worsen. |
| Whealin et al. (111) | Dynamic interplay between PTSD symptoms and post-traumatic growth in older military veterans | Cohort 1 Baseline, Wave 2, and Wave 3 ($n = 2,006$) | Post-traumatic stress disorder symptoms had strong associations with both current and subsequent post-traumatic growth, with the relationship optimally characterized by a non-linear, "inverted U" shaped association in which moderate PTSD symptoms are associated with the greatest gains in PTG over time. | Interventions to promote deliberate, constructive attempts to manage chronic PTSD symptoms via active and religious coping may help promote greater post-traumatic growth in trauma-exposed veterans |

with greater PTG and other protective factors, such as increased purpose in life and dispositional gratitude, thus underscoring the potential importance of religiosity/spirituality in contributing to psychological resilience in U.S. veterans.

## Post-traumatic Growth

A growing body of literature has found that individuals who experience a wide range of traumatic life events (e.g., prisoners of war, refugees, assault survivors, combat veterans) often report experiencing PTG. However, the relationship between PTSD symptoms and PTG is less clear. In the first known nationally representative study of PTG in veterans, Tsai et al. (105) found that nearly three-quarters of veterans who screened positive for PTSD reported at least moderate levels of PTG. Several psychosocial factors, such as greater social connectedness, intrinsic religiosity and purpose in life, were also independently

related to greater PTG (105). Furthermore, they observed a curvilinear (i.e., inverted U-shaped) relationship between PTSD symptoms and PTG, with veterans with a moderate level of PTSD symptoms reporting the greatest levels of PTG. A follow-up prospective study (106) examined whether PTG may predict greater resilience to subsequent traumatic stress. Results indicated that greater scores on the personal strength domain of PTG, which assesses one's perception of their ability to handle difficulties, was associated with reduced severity and incidence of PTSD at a 2-year follow-up (106). Other research on PTG using NHRVS data has found that greater PTG moderates the influence of PTSD on perceived QOL in veterans with life-threatening illness or injury, with higher levels of PTG associated with higher QOL among veterans with greater severity of PTSD symptoms (110).

To date, the vast majority of studies of PTG have been cross-sectional in nature, thus little is known about the longitudinal course or predictors of PTG. Consistent with the cross-sectional studies, a recent prospective study (111) of the dynamic interplay between PTSD symptoms and perceived PTG found that the relationship between PTSD and PTG over time was optimally characterized by a non-linear, "inverted U" shaped association, and that greater severity of PTSD symptoms, particularly avoidance and hyperarousal, were associated with greater PTG over time, but not vice versa. Another study of PTG in the NHRVS found that over a 2-year period, PTSD symptoms, particularly re-experiencing symptoms, greater number of medical conditions, stronger purpose in life, altruism, and an active lifestyle predicted a maintenance or increase in PTG over time (104). Using 4-year prospective data, Tsai and Pietrzak (109) identified three predominant PTG trajectories (i.e., low and decreasing, consistently moderate, and high and increasing) among veterans in hopes of better understanding the temporal course of PTG. Veterans who reported experiencing greater severity of PTSD symptoms, particularly re-experiencing and avoidance symptoms, were more likely to have consistently moderate or high and increasing PTG (109).

## Clinical Implications

In clinical settings, individuals with trauma-exposure generally receive treatments designed to reduce negative symptoms; however, a growing body of research suggests the potential importance of additionally considering interventions designed to foster resilience and PTG (110). Specifically, prevention and treatment efforts designed to enhance modifiable factors such as sense of purpose and meaning in life, dispositional gratitude, and altruism may help promote resilience and PTG in trauma-exposed veterans (104, 107, 109). Further, promoting positive health behaviors (e.g., regular physical activity), and screening and treating medical and mental health conditions may also help bolster psychological resilience and PTG. Furthermore, since re-traumatization is common in trauma-exposed individuals, fostering PTG in clinical settings may help promote psychological resilience in response to subsequent traumatic life events.

# GENETICS AND EPIGENETICS

Many major psychiatric disorders have high heritability. To date, twelve studies (see **Table 6**) have investigated genetic factors associated with major psychiatric disorders such as PTSD and MDD in the NHRVS sample. These studies provide preliminary insight into how genetic factors may increase risk for lifetime PTSD and related disorders in European-American veterans, as well as how environmental factors such as trauma burden and social support may exacerbate or moderate risk for these disorders. Of note, however, results of these studies should be interpreted with caution for the following reasons: first, they primarily focused on candidate genes previously found to be associated with PTSD and related disorders that have not emerged as statistically significant in recent genome-wide association studies; second, they included only European-Americans; and third, they were based on relatively small samples, which were underpowered for genome-wide association studies.

In addition to genetic and gene-by-environment studies, we examined how psychological factors may be linked to markers of biological aging, such as telomere length and DNA methylation age, in veterans. As with candidate gene findings, these findings should be interpreted with caution, as they may be tissue-specific (i.e., derived from cells present in saliva).

## FK506 Binding Protein 5

Examining the interactive effects of candidate genes and environmental factors on risk for mental disorders such as PTSD, rather than investigating independent genetic or environmental influences, may help advance understanding of the etiology of these conditions. Common single nucleotide polymorphisms (SNPs) in the FK506 Binding Protein 5 (*FKBP5*) gene may interact with childhood abuse to increase risk of developing PTSD (123–125). Results from Watkins et al. (113) suggested that the main effects of four *FKBP5* SNPs (rs9296158, rs3800373, rs1360780, rs9470080) were associated with lifetime severity of PTSD symptoms in veterans from C1 and C2 of the NHRVS. Results of this study further revealed that *FKBP5* polymorphisms, directly and interactively with childhood abuse, predicted greater severity of lifetime PTSD symptoms, specifically hyperarousal symptoms.

Building upon these findings, Tamman et al. (122) examined attachment style as a potentially modifiable environmental moderator of this association. A majority of individuals that experience abuse during childhood endorse insecure attachment styles (126), which has in turn been linked to increased risk for PTSD (127). Attachment style is also clinically relevant given that an insecure attachment style has been linked to reduced treatment response among veterans with PTSD (128). This study found that *FKBP5* SNPs, childhood abuse, and insecure attachment style were associated with greater PTSD symptoms (122). Importantly, *FKBP5* homozygous minor allele carriage and history of childhood abuse was associated with greater PTSD symptoms, but these effects were fully counteracted by secure attachment style (122).

**TABLE 6 |** Genetics and epigenetics.

| Citation | Title | Sample | Findings | Clinical implications |
|---|---|---|---|---|
| Pietrzak et al. (112) | Association between negative age stereotypes and accelerated cellular aging: Evidence from two cohorts of older adults | Cohort 1 ($n = 335$) | Negative age stereotypes predicted shorter telomere length in veterans age 60 and older. | Since negative age stereotypes can be modified, such interventions may help prevent premature cellular aging as well as age-related functional decline. |
| Watkins et al. (113) | FKBP5 polymorphisms, childhood abuse, and PTSD symptoms: Results from the National Health and Resilience in Veterans Study | Cohort 1 ($n = 1, 585$) and Cohort 2 ($n = 577$) | *FKBP5* polymorphisms and childhood abuse may contribute to vulnerability for PTSD symptoms and may be most strongly associated with trauma-related hyperarousal symptoms that comprise this phenotype. | Findings may be useful in informing etiologic models of PTSD, by linking these candidate *FKBP5* polymorphisms to specific PTSD symptom clusters, most notably hyperarousal symptoms |
| Watkins et al. (114) | Hostility and telomere shortening among U.S. military veterans: Results from the National Health and Resilience in Veterans Study | Cohort 1 ($n = 484$) | Hostility, specifically, difficulties controlling anger, was associated with peripheral telomere shortening. | Results underscore the importance of assessing anger and aggression among veterans with high levels of hostility. Cognitive behavioral anger management treatments may be helpful in mitigating elevated hostility and associated acceleration of biological aging. |
| Andersen et al. (115) | Polygenic scores for major depressive disorder and risk of alcohol dependence | Cohort 1 ($n = 2,036$) | Higher major depression polygenic risk scores were associated with a significantly increased risk of alcohol dependence. | Findings suggest that common genetic factors contribute to MDD-AD comorbidity and that some individuals carry a genetic predisposition for both disorders. |
| Sippel et al. (116) | Oxytocin receptor gene polymorphisms, attachment, and PTSD: Results from the National Health and Resilience in Veterans Study | Cohort 1 ($n = 1,657$) and Cohort 2 ($n = 506$) | Insecure attachment style and the interaction of *OXTR* rs53576 and attachment style were associated with probable lifetime PTSD | Findings may inform biosocial models of PTSD and suggest that individuals with one or more *OXTR* rs53576 alleles may benefit from interventions that target the oxytocin system and efforts to improve attitudes and feelings toward relationships to facilitate social coping. |
| Watkins et al. (117) | Association between functional polymorphism in neuropeptide Y gene promoter rs16147 and resilience to traumatic stress in US military veterans | Cohort 1 ($n = 1,585$) and Cohort 2 ($n = 557$) | The T allele of *NPY* gene promoter rs16147 was associated with resiliency to cumulative traumatic stress, especially resilience to intrusive symptoms. | *NPY* rs16147 T allele carriers may be less physiologically reactive to trauma cues, because they produce greater levels of NPY during stress. Further research is needed to evaluate whether interventions designed to enhance NPY levels1 may help promote stress resilience in trauma-affected populations. |
| Mota et al. (118) | Apolipoprotein E gene polymorphism, trauma burden, and post-traumatic stress symptoms in U.S. military veterans: Results from the National Health and Resilience in Veterans Study | Cohort 1 ($n = 1,386$) and Cohort 2 ($n = 509$) | The interaction of *APOE* epsilon4 carrier status and cumulative trauma burden was associated with greater severity of PTSD symptoms. Greater social support was associated with lower severity of PTSD symptoms among *APOE* epsilon4 allele carriers with greater cumulative trauma burden. | Enhancement of social support networks among highly trauma-exposed veterans at elevated genetic risk for PTSD may help mitigate PTSD symptoms |
| Averill et al. (119) | Apolipoprotein E gene polymorphism, post-traumatic stress disorder, and cognitive function in older U.S. veterans: Results from the National Health and Resilience in Veterans Study | Cohort 1 ($n = 1,386$) and Cohort 2 ($n = 509$) | APOE epsilon4 allele carriers with PTSD had substantially greater cognitive difficulties than epsilon4 carriers without PTSD. | Findings underscore the importance of assessing, monitoring, and treating PTSD in veterans and other trauma-affected populations who are at increased genetic risk for cognitive decline and dementia. |
| Pitts et al. (120) | BDNF Val66Met polymorphism and post-traumatic stress symptoms in U.S. military veterans: Protective effect of physical exercise | Cohort 1 ($n = 1,386$) and Cohort 2 ($n = 509$) | Met allele carriers reported greater severity of lifetime and current PTSD symptoms, specifically re-experiencing symptoms, with a significant interaction between Met carrier status and lifetime trauma load. Exercise moderated the interaction. | Findings suggest that interventions designed to bolster engagement in physical exercise may help mitigate PTSD symptoms in veterans who are Met allele carriers and highly exposed to trauma. |
| Tamman et al. (121) | Accelerated DNA methylation aging in U.S. military veterans: Results from the National Health and Resilience in Veterans Study | Cohort 1 ($n = 1,135$) | Psychosocial factors of lifetime trauma burden, child sexual trauma, and negative beliefs about aging were independently associated with DNA aging. Diabetes, hypertension, and body mass index also emerged as correlates of DNA aging. | Findings underscore the importance of interventions targeting negative beliefs about aging and modifiable factors linked to DNA aging in veterans at increased risk of age-related morbidities and mortality. |
| Tamman et al. (122) | Attachment style moderates effects of FKBP5 polymorphisms and childhood abuse on post-traumatic stress symptoms: Results from the National Health and Resilience in Veterans Study | Cohort 1 ($n = 1,585$) and Cohort 2 ($n = 577$) | Secure attachment style fully counteracted the significant interaction of *FKBP5* homozygous minor allele carriage and history of childhood abuse that was associated with greater severity of PTSD symptoms. | Results suggest that treatment designed to promote a secure attachment style may help counteract the deleterious interactive effect of *FKBP5* polymorphisms and childhood abuse and help mitigate risk for PTSD. |
| Pitts et al. (120) | Depression and cognitive dysfunction in older U.S. military veterans: Moderating effects of BDNF Val66Met polymorphism and physical exercise | Cohort 1 ($n = 1,386$) | The detrimental effect of depression on cognitive functioning was moderated by two factors known to alter BDNF function the brain: *BDNF* Val66Met genotype and physical exercise. | For veterans at risk of cognitive dysfunction, prevention and treatment efforts designed to promote physical exercise may help preserve cognitive functioning. |

## Neuropeptide Y

Another gene of relevance to traumatic stress and resilience is the neuropeptide Y (*NPY*) gene, which is expressed in a number of brain regions and plays a key role in the regulation of fear, stress, anxiety, learning, and memory (129). Previous studies have found that the rs16147 SNP, which is located in the promoter region of the *NPY* gene and accounts for more than half of the *in vivo* plasma expression of NPY, may interact with traumatic or stressful experiences to predict PTSD symptoms (130). Watkins et al. (117) examined whether polymorphisms in this gene may be linked to resilience to traumatic stress and PTSD symptoms in the C1 genetic subcohort of the NHRVS. Results of this study suggested that the T allele of *NPY* rs16147 was associated with greater resilience to PTSD symptoms, particularly re-experiencing/intrusive symptoms, even in veterans exposed to very high levels of trauma. Further research is need to evaluate whether interventions designed to enhance NPY expression levels, such as intranasal NPY (131, 132) may help promote stress resilience in trauma-exposed individuals (117).

## Apolipoprotein E

The apolipoprotein E (*APOE*) gene has also been implicated in PTSD risk. This gene is active in neuronal repair via cholesterol metabolism and transportation (133). This gene has also been associated with greater probability of developing neurologic and psychiatric disorders (133). Previous research examining the association between *APOE* gene polymorphism and PTSD risk has been mixed due to small and select samples. Accordingly, Mota et al. (118) used data from the genetic subcohorts of C1 and C2 of the NHRVS, and examined the relation between *APOE* genotype and PTSD symptoms. In both C1 and C2 of the NHRVS, the interaction of *APOE ε*4 carrier status and cumulative trauma burden was associated with higher PTSD symptoms, particularly re-experiencing/intrusion symptoms. Notably, they also observed an environmental moderation effect of social support, with greater social support associated with lower severity of PTSD symptoms among *APOE ε*4 allele carriers with greater cumulative trauma burden.

The ε4 allele of the *APOE* gene may also increase risk of cognitive dysfunction among normal aging veterans (134), especially given PTSD is associated with cognitive decline and difficulties (135). Accordingly, Averill et al. (119) examined the effects of *APOE* ε4 genotype and PTSD on cognitive functioning in veterans from C1 and C2 of the NHRVS, as well as a younger, predominantly civilian, replication sample from the Yale–Penn Study. Results revealed that *APOE* ε4 allele carrier status and PTSD were independently associated with lower cognitive functioning in the NHRVS samples (119). Specifically, veterans with PTSD who were ε4 carriers scored lower than those without PTSD, and the most pronounced differences were observed in executive function and attention/concentration. The significant interaction of ε4 and PTSD in predicting executive function was also replicated in the Yale–Penn cohort, but the main effects of ε4 and PTSD were not. Results of these studies suggest that *APOE* ε4 allele carrier status may contribute to the genetic etiology of PTSD symptoms and cognitive difficulties in U.S. veterans. They further highlight the role of trauma burden and social support in moderating the effect of ε4 on PTSD symptoms, and of PTSD in moderating the effect of ε4 on cognitive difficulties.

## Oxytocin Receptor

Polymorphisms in the oxytocin receptor gene (*OXTR*) may also interact with attachment style to predict PTSD, as the oxytocin system plays a key role in social behavior and stress regulation (136). Results from Sippel et al. (116) revealed that insecure attachment style and the interaction of the *OXTR* SNP rs53576, which has been implicated in empathy, loneliness, and parental sensitivity, and attachment style were associated with probable lifetime PTSD. Specifically, veterans with an insecure attachment style were at significantly increased risk of screening positive for PTSD if they had at least one rs53576 A allele, which has been linked to reduced empathy. However, the *OXTR* rs53576 genotype was not associated with PTSD when tested using a GWAS approach in a civilian sample. However, this GWAS did detect a new associated SNP (rs2300549), which was then tested in the veteran NHRVS sample, and while the main effect was null, there was preliminary evidence that it also interacted with attachment style to predict PTSD. Taken together, results of this study indicated that polymorphisms in the *OXTR* gene and attachment style may contribute to vulnerability to PTSD in veterans.

## Brain-Derived Neurotrophic Factor

Genetic studies from the NHRVS have also implicated a specific polymorphism in the brain-derived neurotrophic factor (*BDNF*) gene as a potential risk factor for PTSD (137, 138). BDNF is also know to influence synaptic plasticity, differentiation, and neuronal function. Prior research has found that Met allele of the Val66Met polymorphism of the *BDNF* gene is associated with impaired fear extinction, as well as reduced hippocampal volume and function, in individuals with PTSD (139, 140). Physical exercise has been linked to increased memory function, plasma BDNF levels, and hippocampal neurogenesis (120, 141). Physical exercise has also been linked to reduced depressive and PTSD symptoms (120, 141). To evaluate if physical exercise moderates the effect of the Val66Met SNP on risk of PTSD, Pitts et al. (141) examined the relationship between *BDNF* Val66Met Met allele carrier status, physical exercise, and PTSD symptoms in the NHRVS genetics subcohort. The authors found that relative to Val/Val homozygotes, Met allele carriers reported greater severity of lifetime PTSD symptoms and Met allele carriers with a higher number of traumas reported greater severity of PTSD symptoms (141). Greater engagement in physical exercise moderated this association where, among veterans with high trauma burden, Met allele carriers who engaged in regular physical exercise had significantly lower severity of PTSD symptoms relative to those who did not exercise (141). Another study examined the direct and interactive effect of the *BDNF* Val66Met polymorphism, depression, and physical exercise in predicting cognitive functioning in the NHRVS genetics subcohort (120). Pitts et al. (120) found that depression was associated with moderate decrements in cognitive functioning and this association was moderated by the *BDNF*

Val66Met genotype and physical exercise. Jointly, results of these studies suggest that physical exercise interventions may help mitigate PTSD symptoms in trauma-exposed veterans and cognitive dysfunction in depressed veterans who are Met allele carriers.

### Genome-Wide Association Study of Depression and Alcohol Dependence

Alcohol-related problems, such as alcohol dependence, and MDD are other mental health disorders that are common in genetics research, as it is hypothesized that shared genetic factors may predispose individuals to both alcohol dependence and MDD. Using four genome-wide association study (GWAS) data sets, including C1 from the NHRVS, Andersen et al. (115) examined whether alcohol dependence and MDD have genetic overlap using polygenic risk scores. Polygenetic risk scores quantitatively measure the cumulative effects of common genetic variations across the genome in consideration of risk for a disorder. Results of this study revealed that higher MDD polygenic risk scores were associated with an increased risk for alcohol dependence (115). Results also suggested that there are common genetic factors which contribute to comorbid MDD-alcohol dependence, and that some individuals carry a genetic predisposition for both disorders (115). Findings from this study add a significant contribution to better understanding co-occurring disorders in veterans.

### Telomere Length and DNA Methylation Age

In addition to characterization of genetic risk factors for PTSD, alcohol dependence, and MDD, characterization of factors that may accelerate biological aging is important. Telomeres are nucleoprotein structures that cover the ends of chromosomes and protect from damage (142). Importantly, telomere length is associated with aging-related medical conditions and mortality, in addition to being an indicator of an individual's biological age (142). Hostility is characterized by aggressive urges/impulses and difficulties controlling anger (143). Research has established that hostility is prevalent among veterans (72) and is associated with aging-related disorders and telomere shortening (144). Using data from the NHRVS, Watkins et al. (114) found that greater severity of hostility, particularly difficulties controlling anger, was associated with peripheral telomere shortening in veterans.

Another study (112) evaluated whether negative age stereotypes, which have been linked to increased rates of physical decline, cognitive decline, and mortality in older adults (65, 145), are associated with shorter telomere length in veterans from the NHRVS and an independent sample of civilian older adults who recently experienced an acute myocardial infarction. In both samples, negative age stereotypes were associated with shorter telomere length, independent of sociodemographic characteristics and physical and mental-health indicators.

Aging has also been associated with predictable changes in DNA methylation. Genome-wide methylation research has established algorithms that estimate chronological age and serve as an "epigenetic clock" (146). These estimates, called DNA methylation (DNAm) age, can be used to quantify if DNAm aging is accelerated within an individual, which can predict detrimental health outcomes and is associated with sociodemographic, health, and psychosocial characteristics (121). Specifically, Tamman et al. (121) found that three physical health variables—diabetes, hypertension, and body mass index—were associated with accelerated DNAm aging. Cumulative trauma burden, child sexual trauma, and negative beliefs about aging were additionally associated with accelerated DNAm aging. Notably, child sexual abuse explained nearly the same amount of variance in accelerated DNAm age as diabetes (33.2 vs. 35.9%), thus underscoring the importance of trauma exposure in the acceleration of DNAm age. These results suggest that prevention and treatment efforts to mitigate deleterious effects of trauma exposure and negative beliefs about aging, which are modifiable, may help forestall accelerated DNA methylation aging in veterans.

### Clinical Implications

Collectively, results of NHRVS genetic and epigenetic studies underscore the utility of assessing, monitoring, and treating trauma-exposure, specifically childhood abuse and cumulative trauma burden, in veterans with certain genetic polymorphisms (113, 118–120, 122). They further suggest that therapeutic enhancement of modifiable protective factors, such as social support networks (e.g., one-to-one mentorship programs, peer support groups, social/relationship skills interventions, Vet-to-Vet programs), attachment style, and physical exercise among trauma-exposed veterans at elevated genetic risk for PTSD and related disorders may be an important aspect of prevention initiatives (116, 120, 122). Further, prevention and treatment efforts designed to reduce implicit negative age stereotypes, and anger and hostility may help mitigate acceleration of biological aging, and ultimately help reduce risk for age-related disorders among veterans (112, 114). As noted above, however, these findings must be interpreted with caution and require replication in larger, more diverse samples, as well as in tissues other than saliva.

## CONCLUSIONS AND FUTURE DIRECTIONS

This narrative review summarized results of 82 original research studies that have been published to date using data from the NHRVS. These studies have covered six major topic areas, including post-traumatic stress disorder, suicidality, aging, resilience and post-traumatic growth, special topics relevant to veterans, and genetics. Collectively, the results of these studies underscore the need to develop and test prevention and intervention strategies that aim to enhance modifiable protective factors in veterans. Just as risk factors may have additive and interactive effects, such that having multiple genetic, developmental, neurobiological, and/or psychosocial risk factors may increase allostatic load or stress vulnerability, having and enhancing multiple protective factors may help promote stress resilience (147). Prior research prevention and intervention strategies designed to enhance these protective factors have been limited to community samples and have received little to no empirical support (4, 148, 149). Results of NHRVS studies published to date suggest that interventions that aim to assist

veterans in building social connections and becoming better integrated in their communities, such as interventions that promote volunteerism (150) and reduce loneliness (151, 152) may help enhance resilience among veterans and warrant further investigation (153).

Extant research from the NHRVS has covered a broad range of health issues of relevance to U.S. military veterans. In future research in the NHRVS, including a new cohort of more than 4,000 veterans who completed a baseline NHRVS survey in 2019–2020, we plan to examine other conditions that may co-occur with PTSD, such as attention-deficit/hyperactivity disorder, traumatic brain injury, chronic pain, and dementia. Despite the inclusion of numerous potential correlates in the initial two NHRVS cohorts, there are other relevant factors, such as a broader range of potentially traumatic experiences that were not assessed in these cohorts, that may be differentially associated with PTSD and related disorders. Additionally, the assessment of substance use (e.g., cannabis and AUD), as well as suicidality and non-suicidal self-harm behaviors has been expanded in this new cohort.

Information on genetic, epigenetic, and modifiable protective factors, such as social connectedness, attachment style, physical exercise, have the potential to be combined to develop clinically useful risk-prediction models for PTSD and related disorders. Each of these factors alone may be weakly or moderately informative when considered individually, but a combination of these factors may provide more integrative approaches for assessment, monitoring, and treatment to mitigate risk for mental disorders that are prevalent in veterans, and promote better functioning and QOL in veterans. Accordingly, a goal for future NHRVS studies is to employ advanced data analytic approaches such as machine learning to identify key combinations of psychological, social, and biological (i.e., genetic) factors linked to key health outcomes in veterans.

Longitudinal epigenome-wide association studies (EWAS) are also being planned to examine the stability and predictive utility of epigenetic (e.g., DNA methylation) changes associated with PTSD and related disorders in the NHRVS genetics subcohorts. Although longitudinal EWAS are expensive and difficult to conduct, cross-sectional studies cannot detect the dynamic nature of epigenetic mechanisms impacting complex and evolving psychiatric disorders such as PTSD, making it difficult to ascertain whether the underlying causal effect is environmental or genetic (154). These studies may also provide insight into time- or condition-varying effects in veterans (155).

In summary, NHRVS studies published to date have yielded several important new findings regarding the psychosocial and genetic epidemiology of mental disorders, suicidality, aging, resilience, and post-traumatic growth. Specifically, veterans report exposure to a wide range of potentially traumatic events and a considerable proportion of veterans report experiencing PTSD, MDD, AUD, and related symptoms in their lifetime. However, a majority of veterans were found to be psychologically resilient in later life. Results suggest that initiatives designed to promote protective psychosocial characteristics (i.e., resilience, gratitude, purpose in life) and social connectedness (i.e., secure attachment, community integration, social engagement) may help promote resilience and growth in veterans, and may help mitigate risk for prevalent mental disorders in this population.

Given the nationally representative nature of the NHRVS, these findings can directly inform population-based prevention and treatment efforts in the broader U.S. veteran population. Many of the findings may also be applicable to the general U.S. adult population, as the majority of the NHRVS cohorts were comprised of non-combat-exposed veterans. Further research is needed to examine how demographic changes in the veteran population, including race and ethnic factors, older age, and a larger proportion of female veterans, may influence mental, physical, and cognitive health outcomes over time; and to translate findings from the NHRVS and other large-scale epidemiologic studies of veterans into novel and targeted prevention and treatment strategies to mitigating risk for major health conditions, and preserving functioning and overall quality of life in this population.

## AUTHOR CONTRIBUTIONS

BF was responsible for the formal analysis and writing, and original draft preparation. JT, NM, IH-R, JK, and SS contributed to writing, review, and editing of the manuscript. RP supervised and contributed to the conceptualization, investigation, analysis, data curation, writing, review and editing, and funding acquisition. All authors discussed the results, contributed to the writing, and approved the final manuscript.

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# Enhancing Health Care in the Veteran Community Through Synergistic Research Funding

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The veteran population faces myriad health burdens, particularly regarding mental health. As veterans age, combined genetic, environmental, and biochemical factors with natural biological processes may increase their susceptibility to mental health disorders as well as neuropsychiatric and dementia-related disorders that present as persistent cognitive impairment. Multi-organizational, multidisciplinary research partnerships help explore relevant evidence-based methodologies and create a two-way continuum between basic science and clinical application to address veterans', often complex, health care needs. The Congressionally Directed Medical Research Programs (CDMRP), a global funding organization located within the U.S. Army Medical Research and Development Command (USAMRDC), fosters novel approaches to biomedical research in response to the expressed needs of stakeholders and, as directed by Congress, many CDMRP programs focus on topics that are relevant to the health care of veterans. The CDMRP's foundation as a research management organization includes a two-tier review process and fully integrates consumer advocates. The CDMRP complements the U.S. Department of Veterans Affairs (VA) research through collaborative partnerships and synergistic award mechanisms tailored to areas of greatest need. Continued partnerships between the VA and CDMRP can facilitate translation of basic research to clinical application and enhance health care in the veteran community. This perspective highlights the need for research to address mental health issues affecting the veteran community, describes how the CDMRP integrates veterans into its processes, and discusses how the CDMRP's processes and collaborations with the VA have the capacity to improve mental health care for veterans.

**Keywords: research and development, veteran health, veterans, mental health, biopsychosocial research**

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## INTRODUCTION

Service members and veterans experience military-specific stressors that require focused research. Results from research conducted with the general population, therefore, may not translate to these subpopulations. Research and collaboration to address mental health conditions and to promote resilience among service members and veterans are priorities within the Department of Defense (DOD) and VA (1).

The veteran population faces numerous and significant health burdens. Specifically, veterans experience traumatic brain injury (TBI) and mental health disorders at disproportionate rates

compared to their non-veteran counterparts (2). In a large Veterans Health Administration primary care sample, the prevalence of post-traumatic stress disorder (PTSD), substance use disorder, anxiety, and serious mental illness was higher than that of the general population (3). Individuals with PTSD often experience other physical and mental health comorbidities that increase the complexity of treatment and the burden on patients. Among Operation Enduring Freedom/Operation Iraqi Freedom veterans, alcohol dependence and PTSD are particularly comorbid (4). As veterans age, environmental conditions, genetics, and biochemistry, combined with naturally occurring biological processes, may make them more susceptible to neuropsychiatric and dementia-related disorders as well (5). For example, evidence suggests that veterans with PTSD are at increased risk of developing dementia, though the mechanisms linking these disorders are not fully understood (6). Mental health stigma, which may be unintentionally amplified by military culture, is a barrier to care that further complicates assessment and treatment of mental health disorders (7). The complex interplay among these factors highlights the need for focused research to address the health care needs of veterans.

Multi-organizational, multidisciplinary research partnerships fostered by the CDMRP are well-positioned to address the many complexities with veteran healthcare. The purpose of this perspective is threefold: (1) to describe how key facets of the CDMRP's program cycle integrate veterans and veteran health care perspectives, (2) to discuss the importance of collaborative partnerships and synergy between the CDMRP and the VA when reviewing and conducting veteran-focused scientific research, and (3) to promote the bi-directional translation of basic science to clinical application to improve veteran mental health.

## CDMRP OVERVIEW

The CDMRP is a directorate located within the USAMRDC that manages over 35 biomedical research programs, as directed by Congress (see **Table 1**). The mission of the CDMRP is to responsibly manage collaborative research that discovers, develops, and delivers health care solutions for service members, veterans, and the American public. The CDMRP fosters novel approaches to research and brings together diverse groups of stakeholders that otherwise may not collaborate. Co-location with the Army acquisition framework enables a low management rate, allowing >90% of appropriated dollars to be invested in research.

The CDMRP's research management model includes targeted funding opportunity announcements and active engagement with patients, including veterans, living with health conditions. Veterans weigh in on program policy, investment strategy, and research focus. This model enables a two-way continuum between basic science and clinical application and promotes promising approaches to advance research and enhance healthcare in the veteran community. Using complementary funding opportunity announcements and synergistic funding mechanisms that encourage collaboration, the CDMRP and the VA have the capacity to better harness the power of research and evidence and make sure it is translated into action.

**TABLE 1 |** CDMRP managed and supported programs and FY 2020 appropriations.

| CDMRP program | FY2020 appropriation, $ million |
|---|---|
| Amyotrophic Lateral Sclerosis | $20.0 |
| Alzheimer's | $15.0 |
| Autism | $15.0 |
| Bone Marrow Failure Disease | $3.0 |
| Breast Cancer | $150.0 |
| Breast Cancer Research Semipostal | TBD |
| Chronic Pain Management | $15.0 |
| Combat Readiness Medical | $10.0 |
| Duchenne Muscular Dystrophy | $10.0 |
| Epilepsy | $12.0 |
| Gulf War Illness | $22.0 |
| Hearing Restoration | $10.0 |
| Joint Warfighter Medical | $40.0 |
| Kidney Cancer | $40.0 |
| Lung Cancer | $14.0 |
| Lupus | $10.0 |
| Melanoma | $20.0 |
| Military Burn | $10.0 |
| Multiple Sclerosis | $16.0 |
| Neurofibromatosis | $15.0 |
| Orthotics and Prosthetics Outcomes | $15.0 |
| Orthopedic | $30.0 |
| Ovarian Cancer | $35.0 |
| Pancreatic Cancer | $6.0 |
| Neurotoxin Exposure Treatment Parkinson's | $16.0 |
| Peer Reviewed Cancer (14 topics) | $110.0 |
| Peer Reviewed Medical (44 topics) | $360.0 |
| Prostate Cancer | $110.0 |
| Rare Cancers | $7.5 |
| Reconstructive Transplant | $12.0 |
| Scleroderma | $5.0 |
| Spinal Cord | $40.0 |
| Tick-Borne Disease | $7.0 |
| Tuberous Sclerosis Complex | $6.0 |
| Vision | $20.0 |
| **Additional supported DOD programs/projects[a]** | |
| Armed Forces Institute of Regenerative Medicine | TBD |
| Defense Medical Research and Development | $232.1 |
| Psychological Health/Traumatic Brain Injury | $165.0 |
| Small Business Innovation Research/Small Business Technology Transfer | TBD |
| Trauma Clinical | $10.0 |

[a] *Approximate funding of additional supported DOD programs/projects.*

## CDMRP PROGRAM CYCLE

Each CDMRP-managed program has individually tailored goals and a distinct vision enabling funded research to

meet the specialized needs of the research and patient communities. Several programs focus on mental health and other topics relevant to veteran health care, and opportunities for collaboration with the VA exist throughout the program cycle (see **Figure 1**).

The first major milestone in the cycle is the Vision Setting meeting, during which the Programmatic Panel convenes to assess the research landscape and develop an investment strategy. Each Programmatic Panel is comprised of a multidisciplinary group of research scientists, clinicians, foundations, industry, other federal agencies [such as the VA and National Institutes of Health (NIH)], and consumer advocates. For example, the Alcohol and Substance Abuse Disorders Research Program (ASADRP) Programmatic Panel consists of members from the U.S. Army, the National Institute on Alcohol Abuse and Alcoholism, the National Institute on Drug Abuse, and the Department of Veterans Affairs. Based on knowledge from their respective portfolios, the ASADRP Programmatic Panel recommended at a recent Vision Setting meeting an investment in multi-institutional research consortia involving teams of leading scientists and clinicians working together under one umbrella to identify pharmacotherapies that address alcohol and substance abuse disorders, with an emphasis on those related to TBI and PTSD in service members and veterans.

After establishing the program vision and investment strategy, Program Announcements are developed to solicit research applications that will make a significant and non-incremental impact (8). CDMRP uses a two-tier review process, recommended by the National Academy of Medicine, to identify research proposals that target program goals while also capturing the traditional strengths of scientific merit peer review systems. Initially, applications are evaluated for scientific and technical merit against criteria published in the funding opportunity. This first review is conducted by a scientific peer review panel consisting of scientists, clinicians, administrators from the VA and other stakeholder organizations, and consumers, independent of those serving on the Programmatic Panel. Scientific merit peer review is followed by a comparison-based programmatic review conducted by the Programmatic Panel. Although the ratings and evaluations of the peer reviewers are a key factor, programmatic reviewers do not automatically recommend funding applications that were highly rated in the scientific merit review process. Rather, they carefully compare applications ensuring proposals that have high potential to achieve the goals of the respective program and that contribute to a good portfolio balance are recommended for funding. This means that applications are not funded using an established "pay line." At the final step of the program management cycle,

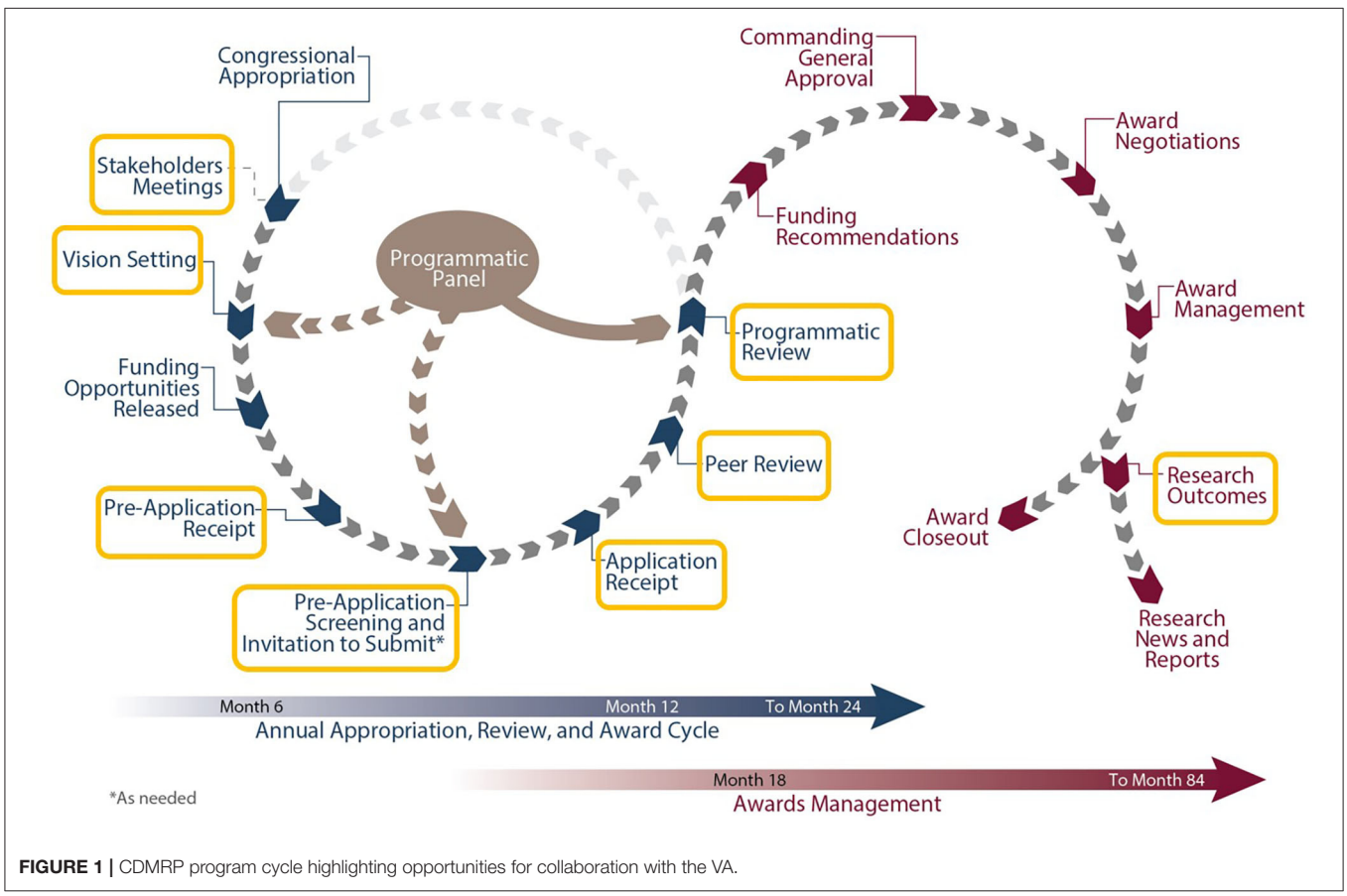


**FIGURE 1 |** CDMRP program cycle highlighting opportunities for collaboration with the VA.

funding recommendations are presented to the USAMRDC Commanding General for approval.

## CDMRP HALLMARKS

A distinguishing CDMRP feature is the significant involvement from consumer advocates such as patients, survivors, family members, or caregivers impacted by the disease, condition, or injury throughout the program cycle. Applications are required to include an impact statement describing how the proposed research, if successful, will significantly advance the field and impact the patient advocate community (8). The potential impact of the proposed research is an important review criterion and consumer advocates hold equal weight to the clinicians, researchers, and other experts on the review panel. For example, consumer advocates involved with the ASADRP include active duty, veteran, or retired service members who have received treatment for alcohol and substance use disorders (ASUDs) related to PTSD and/or TBI and DOD or VA behavioral health providers. These consumer advocates play an important role in maintaining the focus of the ASADRP and provide a unique perspective on issues important to the end user community.

The CDMRP model facilitates investment in high-impact and high-risk/high-gain studies that other agencies may not fund. Unlike other federally funded agencies that receive funding in the President's budget each fiscal year, the CDMRP develops an investment strategy based on additional, individually-directed Congressional appropriations each fiscal year. Due to the nature of funding, multi-year awards are fully allocated up front, ensuring research projects are not put at funding risk. This also allows programs to shift focus year-to-year based on innovative advances in the field without the need to fulfill out-year budgets of previously selected awards. Additionally, the CDMRP uses novel, focused award mechanisms, directed at each disease, condition, or injury specified in Congressional language. For example, the Idea Award was developed by the Breast Cancer Research Program to support research with little or no preliminary data. Supporting early concepts and ideas complemented other Federal funding programs that required preliminary data, supported the next logical step, and were not disease- nor condition-focused (8). This CDMRP award mechanism moved research into new and unchartered territory in the 1990s and continues to be used by CDMRP programs today.

While industry, including pharmaceutical, biotechnology, and medical device firms, remains the largest funder of clinical trial research, the CDMRP's niche in this arena is the encouragement of preventive or therapeutic interventions that are in line with state of the art research and the priorities of the communities affected by the disease. For example, the ASADRP Pharmacotherapies for Alcohol and Substance Abuse (PASA) Consortium establishes pharmaceutical company partners who have compounds for ASUDs or PTSD available, but who need the complement of experts from the PASA to complete human studies to the U.S. Food and Drug Administration's (FDA) standards (9).

While all programs managed or supported by the CDMRP are focused on solutions for service members and the American public, three programs are particularly relevant to veteran health—the Gulf War Illness Research Program (GWIRP), the Psychological Health and Traumatic Brain Injury Research Program (PHTBIRP), and the ASADRP. From 2018 to 2019, the GWIRP, PHTBIRP and the ASADRP yielded ∼500 publications, 20 patents/patent applications, and 50 research products. Furthermore, in a 2018 internal review of 10% of CDMRP-managed clinical trials funded between fiscal year 2008 and fiscal year 2015, 74% of closed trials met the CDMRP-defined criteria for success. These outcomes, as well as the unique aspects of the review and management model described herein, illustrate how CDMRP is able to translate important research results into medical solutions for patient communities.

## COLLABORATIVE PARTNERSHIPS

The CDMRP has formed strong partnerships among the DOD, VA, and patient, scientific, and clinical communities to advance paradigm-shifting research and provide solutions that will lead to cures or improvements in care. CDMRP funding opportunities are open to VA researchers and clinicians as well as those from the military, academia, and the private sector. Inclusion of a military or VA investigator as an equal partner in the research is strongly encouraged in many CDMRP funding opportunities and the degree of this partnership is evaluated during the review process. Partnerships with the military and the VA are important to access relevant active duty and VA patient populations. In addition, the DOD and VA, with participation from the NIH, conduct a joint review and analysis of their portfolios annually.

The collaboration between the GWIRP and the VA is an example of a funding partnership that makes the best possible use of available resources in support of high-quality, veteran-focused research. The GWIRP was established in 2006 when Conferees directed the Secretary of the Army to utilize authorized funding to undertake research on Gulf War Illness (GWI) and to coordinate with similar activities at the VA. GWI is characterized by multiple, diverse symptoms not explained by established medical diagnoses or standard laboratory tests. The GWIRP is the only CDMRP program completely dedicated to veteran health, and frequent communication and collaboration occur between the VA and GWIRP Program Managers (PMs). Specific examples of such collaborations include GWIRP PM participation on VA-convened working groups, VA funding of GWIRP spin-off proposals, sharing of funding data through electronic coordination, and a recent GWI State of the Science conference co-hosted by the VA Office of Research and Development and the GWIRP. In addition, the GWIRP awarded a Clinical Trials Consortium in fiscal year 2017 that includes two of the VA War Related Illness and Injury Study Centers as recruitment sites, further demonstrating collaborative and optimal use of resources.

The CDMRP provides program and award management support for many other consortia that involve partnerships between the DOD, VA, and academia. These large awards bring together multidisciplinary, multi-organizational teams to tackle complex problems affecting service members and veterans such as PTSD, TBI, suicide, and ASUDs. An advantage of the consortium model is the ability to require collection of common data elements and aggregate data from numerous studies into

a single data repository. The CDMRP strongly encourages the sharing of data and research resources generated from CDMRP-funded research, while protecting participant privacy, confidential and proprietary data, and intellectual property. The STRONG STAR Consortium to Alleviate PTSD (CAP), a jointly funded DOD-VA effort, and the Military Suicide Research Consortium (MSRC) are two CDMRP-managed consortia that house data which can be accessed by other researchers who are interested in conducting secondary analyses of de-identified data. Qualified investigators can access the STRONG STAR-CAP[1] and MSRC[2] websites for additional information on how to request access to data.

Strategic direction and oversight of consortia and other large awards is typically provided by Government Steering Committees or External Advisory Boards that include representatives from the DOD, VA, NIH, Centers for Disease Control and Prevention, and/or other relevant stakeholder agencies. This ensures that products resulting from these awards meet the end users' needs. Findings from several studies funded under the MSRC are referenced in the *VA/DOD Clinical Practice Guideline for The Assessment and Management of Patients at Risk for Suicide*, which directly impacts veteran mental health treatment (10).

These collaborative partnerships provide opportunity for greater return on investment and more expedited scientific advances. Coordination with the VA throughout the entire CDMRP program cycle helps ensure that both organizations avoid duplication of effort, stay abreast of developments in the field, and continue to foster collaborative opportunities.

## OPPORTUNITIES FOR SYNERGY ACROSS THE RESEARCH CONTINUUM

Research spans a continuum from discovery to clinical trials before the fielding and clinical application of knowledge and products. The CDMRP uses directed funding mechanisms, targeting specific steps along the continuum of research development, including basic, translational, and clinical research. These innovative funding opportunity announcements also complement research funding at the VA.

VA research funding mechanisms are similar to those used at the NIH and rely primarily on the individual research interests of VA intramural investigators (11). The CDMRP complements VA research through use of synergistic award mechanisms that are tailored to areas of greatest need. While one agency may be better positioned to fund only one component of a project (e.g., basic science), another agency may be better positioned to fund other components (e.g., clinical trial). From 2018 to 2019, for example, GWIRP, ASADRP, and PHTBIRP-funded investigators obtained follow-on funding from the DOD, NIH, VA, and other agencies on more than two dozen occasions.

This type of synergistic funding between the CDMRP and VA is evidenced through GWI treatment investigations. Preliminary analysis from a pilot trial supported by the GWIRP demonstrated, in a subset of veterans with GWI, that 100 mg of coenzyme Q10 (known as CoQ10 or Ubiquinone) improved general self-reported health and physical functioning (12). The results from this pilot trial supported the possibility of efficacy and were the basis for a larger, VA-sponsored Phase III trial initiated in 2017 of Ubiquinol, the reduced form of CoQ10. Parallel to the Phase III trial, the GWIRP funded biomarker analysis both before and after CoQ10 therapy using blood collections from subjects in the clinical trial. Potential biomarkers will be correlated with symptom clusters, illness severity, and predicting responders to the intervention. More recently, the GWIRP invested in a true replication trial, using the same high quality/bioavailability product and validated outcomes that previously showed benefit in the GWIRP-funded pilot study. The VA will use the collective results of these studies to inform Clinical Practice Guidelines and VA Formulary considerations for ill Gulf War veterans.

Within the PHTBIRP, research progress has been accelerated through studies seeking to translate existing interventions initially developed and evaluated with funding from the NIH, VA, or other agencies for military and veteran contexts. Examples include suicide, substance misuse, and sexual assault/harassment prevention interventions originally designed for use with college students and suicide treatment interventions designed for civilian medical settings adapted for use with military and veteran populations (13–15). Tailoring existing evidence-based interventions to meet a specific need significantly reduces the time required before an intervention is able to touch service members' and veterans' lives.

The ASADRP-funded PASA Consortium uses planning grants for clinical trials and full study research grants for pre-clinical trials. This is a novel risk mitigation strategy that allows them to leverage a relatively small appropriation to conduct complex/high risk research involving drug trials on human subjects. The purpose of a planning grant is to create a clinical development plan that includes study protocol development, regulatory pathway development, identification of study sites, pharmaceutical company support, determination of the need for additional studies by the FDA, and a study budget. Once this has been accomplished, the documents are submitted to the PASA and undergo a two-tier review before a funding recommendation is considered. Nine compounds are in pre-clinical trials for alcohol use disorder and PTSD while five other compounds are undergoing clinical review.

These and other CDMRP funding opportunities demonstrate the value of leveraging and maximizing federal dollars to support veteran health. Such synergies can significantly accelerate progress, thus shrinking the pipeline for development of new therapeutics, new diagnostics, and changes in the standard of care.

## CONCLUSION

Multi-organizational, multidisciplinary research partnerships are needed to address the health burdens faced by veterans. Emerging results have the potential to be most impactful if they continue to feed into the two-way continuum between basic science

[1]https://patriot.uthscsa.edu/strongstar/subs/rpinfo.asp?prj=12
[2]https://msrc.fsu.edu/members/request-access-msrc-database

and clinical application to inform patient care and future research priorities.

The CDMRP management model has many integrated activities that rely on partnerships with the VA to ensure translation of basic research to clinical applications. Additionally, the CDMRP fully integrates consumer advocates, including veterans with significant health issues, in program policy, investment strategy, and research focus. Many CDMRP funding mechanisms promote the translation of science from discovery through different development stages, including the transition to clinical studies and product development. Collaborating with the VA early in the development of the program strategy and funding mechanism facilitates translation of innovative and impactful technologies funded by the VA and DOD. This creates new medical solutions for service members, veterans, and the American public. Emphasizing collaboration and stepwise translation may help funding agencies facilitate a seamless transition, capitalize on efficiencies, and reduce costs. Such efforts are integral to improving the mental health of the veteran population and advancing the field.

To learn more about the CDMRP and its programs or to receive funding opportunity notifications by e-mail, please visit https://cdmrp.army.mil.

## AUTHOR CONTRIBUTIONS

ML and KL participated in conceptualization of the article, drafting, and final editing. RS and SD participated in drafting and reviewing the article. All authors approved the final version of the manuscript to be published and agreed to be accountable for all aspects of the work.

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# Demographic, Health, and Exposure Risks Associated With Cognitive Loss, Alzheimer's Disease and Other Dementias in US Military Veterans

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The US military veteran population receiving care through the Veterans Health Administration (VHA) is particularly susceptible to cognitive impairment and dementias such as Alzheimer's disease and related dementias due to demographic, clinical, and economic factors. In this report we summarize the prevalence of dementia among US veterans and risks associated with AD and related dementias. We discuss the likelihood that these risks may be increasing in those about to enter the age in which dementias are common. We propose that VHA, the largest integrated health care system in the US, has shown promise in managing health risks that impact dementia prevention and propose further system wide approaches to be assessed for effective dementia prevention and care delivery.

**Keywords: Alzheimer's disease, dementia, veterans, risk, risk management**

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The US veteran population is aging and at increased risk of developing chronic neurodegenerative diseases such as Alzheimer's disease and related dementias. As of 2020, the Veterans Health Administration (VHA) provides comprehensive medical care for more than 9 million enrolled veterans at its 1,255 facilities, including 172 medical centers, and more than 1,074 outpatient clinics across the country. More than half of the patients in the VA are age 65 or older (1, 2). Changes in demographic characteristics such as more women and more diverse veteran populations may lead to a veteran population at higher risk of dementia. Several risks factors for dementia identified in the general population may be more prevalent in the Veteran population. Additionally, Veterans' risks for dementia can also be influenced by changes in VA policies on eligibility and enrollment criteria, and factors external to the VA. In this report, we summarize identification and prevalence of dementia in the VA, and current knowledge of demographic, health, and military related risk factors of dementia in the VA. The VA has experience in managing cardiovascular diseases, mental health, TBI, PTSD, and conditions that are common among veterans. We propose that VHA, the largest integrated health care system in the US, has promise in managing health risks that may impact dementia prevention and propose further system wide approaches to be assessed for effective dementia prevention and care delivery.

## DEMENTIA PREVALENCE AND IDENTIFICATION IN THE VA

Currently the VHA estimated dementia prevalence among VA patients age 65 and older at 9.6%. A recent meta-analyses of dementia prevalence studies reported a similar pooled prevalence

rate of 10.1% in the VA (3). These estimates are broadly consistent with rates reported in the general population of 10.5% (4, 5). Prevalence of dementia among veterans is expected to increase dramatically in the coming decades (5–8). VHA Office of Policy & Planning projects a 22% increase in the number of VA Patients with Dementia (276,000–335,000) between 2020 and 2033 (5).

Several studies have estimated dementia prevalence among VA patients enrolled in specific programs or settings such as VA nursing homes and specialty mental health programs (9–11). Results from these studies are not directly comparable to those in the general veteran and non-veteran populations because of selection of patients into these programs and differences in patient characteristics (e.g., VA continues to care for a younger, more functionally disabled nursing home population than the non-VA population).

## Identification of Dementia in VA Administrative Data

Identification of dementia is complicated by many factors. There is substantial under-recognition, under-diagnosis, and under-recording of dementia in many systems. As much as 50% of dementia cases are un-identified in primary care settings (12, 13). One study in the VA suggested that many as 70% of the estimated veterans with dementia were not readily identified through their medical records (14). The VA has a sanctioned list of ICD codes intended to be used as the standard among all programs and services throughout the system for the purposes of dementia-related data analysis and reporting, including workload, cost, incidence, prevalence, forecasting (15), however it has not been used consistently across studies to identify dementia in the VA, making comparisons between studies difficult (9, 10).

In addition to VA care, older veterans have access to care outside the VA through almost-universal eligibility for Medicare, further complicating identification of dementia in the VA. Data from a national sample of VA patients with a formal diagnosis of dementia showed that approximately half of veteran with dementia used both VA and Medicare (16). There is substantial between systems coding disparities of dementia (17–19). In the general Medicare population, fewer than half of beneficiaries who have a clinical diagnosis of AD or related dementias have a recorded diagnosis in their claims (20). A study of VA patients age 65 and older who were enrolled in Medicare FFS in FY2013 showed that only 4.8% of veterans had a dementia diagnosis in VA data (4). Combining VA data with Medicare claims identified 7.4% of veterans with a dementia diagnosis, closer to the dementia prevalence rate of 9.6% among veterans estimated by VHA (21).

Historically, VA has served as a safety net to disabled and low income veterans and continues to serve a veteran population with much greater prevalence of chronic illness (4, 22–25). There are marked differences among veterans who seek care in both VA and Medicare compared to only in the VA. For example, reliance on VA health care was greatest among black veterans and those in high VA priority groups. Veterans with poorer health were most likely to rely on both VA and Medicare (26). Because of their cognitive impairment and dementia, these veterans may be particularly vulnerable to suffer from inferior care and under identification due to uncoordinated care across systems (27, 28). There is some evidence that dementia identification has been improving in recent years (29). In the VA, more consistent use of the VA sanctioned diagnoses along with those from Centers for Medicare and Medicaid Services (CMS) Chronic Condition Warehouse (CCW) (30) will be beneficial to improve dementia identification that is necessary to better care for dementia patients.

# RISKS FACTORS FOR DEMENTIA IN THE VA

## Demographic Factors

The veterans served by the VHA may be at higher risk for dementia than the general population for many reasons, including demographic, health, lifestyle, and military related factors. For example, the veteran population is becoming more diverse than the overall US population with higher percentages of African American and Latinos among veterans. These groups have historically had higher risk of dementia. According to a 2016 report, the prevalence of dementia is 26.6/1,000 among African Americans compared to 19.3/1,000 among non-Hispanic whites (31). Similar disparities between African Americans (19.3/1,000 years) and non-Hispanic whites (10.8/1,000) exist in the veteran population. The proportion of African Americans among younger veterans (those younger than 65) is nearly double that of those 65 or older and they represent an even higher proportion of patients in the VA, suggesting that this demographic risk will increase over the next few decades.

Most studies indicate increased risk of dementia in older women than men of the same age partly because older women typically had less education than older men (32). Although the proportion of women receiving health care in the VA is still low currently it is estimated to be increasing, suggesting potential for future increased risk of dementia in the VA. Several studies described below additionally indicate significant risk for dementia among women who are exposed to military related risks (33). One study reported significantly higher risk of developing dementia in 4 years in women veterans with TBI, PTSD, and depression, and those with more than one risk factor had a >2-fold risk of developing dementia (33).

It is well known that low education increases overall risk for dementia (34). This risk, recently described as an early life modifiable risk factor (32), may possibly be modifiable even later in life, although the evidence for that is not yet well-established. While veterans may have educational opportunities later in life that are not available in the general public, male veterans continue to lag behind non-veterans in obtaining a Bachelor's degree (35). While the opposite is true in female veterans they currently make up a small portion of the veteran population.

## Health Risks

Several comorbid conditions which have been associated with cognitive impairment and dementia appear to be more prevalent among veteran populations. There may be influences specific to veteran status that increase the risk of many conditions

that contribute to cognitive impairment and dementia. For example, in a report from the Health and Retirement Study which examined individuals over 50 without heart disease at initial observation, self-reported veteran status was associated with increased risk of new onset heart disease compared non–veterans. The cohort, which is demographically representative and was tracked during the 20 year period from 1992 to 2012, identified veteran status as a significant risk factor even after controlling for demographic characteristics (age, gender, education, marital status), clinical characteristics (depression, hypertension, diabetes), and lifestyle (smoking, drinking, exercise). While this report did not examine the link between heart disease and cognitive impairment and dementia, others have reported that cardiovascular risks, such as hypertension, dyslipidemia, diabetes, metabolic syndrome, and obesity, all prevalent in veteran populations, are specifically associated with cognitive impairment and dementia (36, 37). The combined cardiovascular risk factors highlight the importance of clustering these factors which have identified dementia risk less readily observed when considered alone (38).

## Mental Health Risks

Mental health disorders such as depression, anxiety, and more recently, alcohol abuse syndromes have been identified as risks for dementia in the general population (32). All of these disorders are common among veterans. Specifically, a quarter of all Veterans seen in primary care at the Patient Aligned Care Teams (PACT) have 1 or more mental illness diagnosis, including depression (13.5%), substance use disorder (8.3%), anxiety disorder (4.8%), or other serious mental illness (3.7%) (39). Veterans also have relatively high estimates of dual diagnosis of these conditions with dementia. While in general the number of active psychiatric conditions decreases with age, they may actually be risks for cognitive impairment and dementia in later life. Depression and anxiety are well-recognized for increasing the risk of dementia and links *via* stress mechanisms have been proposed (40). These mental health conditions are also associated with increased vascular risks as are some of the most common medications used to treat these conditions. For example, studies have shown that depression, psychosis, and bipolar disorder were associated with increased risk of cardiovascular diseases (41). While some classes of medications exacerbated this risk, the effects of the conditions remained after treatment factors were controlled. The prevalence of cardiovascular diseases, metabolic risk factors, and mental health conditions creates a complex of circumstances that increase risks for dementia and make identifying dementia risks challenging.

## Military Related Risks: Head Trauma

Military experience can be associated with significant events that increase health risks in general and cognitive health risks in particular. Head injury, well-established as a risk factor for dementia among the general population (32), is common in military experience (42). Estimates in the recent past showed that over 1.5 million Iraq and Afghanistan veterans have suffered a traumatic brain injury (TBI) during deployment. Mild TBI (mTBI) such as that experienced with blast injury and possibly experienced as a mild concussion is likely to be under-reported (43, 44). A large national study of patients with TBI in the VA found that that mTBI even without loss of consciousness was associated with more than a 2-fold increase in the risk of dementia (45). There is growing evidence that mTBI is potentially causally association with a range of brain related outcomes including PTSD, depression, and other conditions. Preclinical work with animal models supports mechanisms by which mTBI can induce Post-Traumatic Stress Disorder (PTSD), and as discussed below, this may be a path to increased risk of dementia. Clinical work has yet to confirm these models.

## Military Related Risks: Post-traumatic Stress Disorder

The role of early and midlife stress related disorders as a risk factor for dementia have been studied both in military and non-military settings (46–50). Examining a national patient registry in Sweden, the presence of a stress related disorder, including PTSD, acute stress reaction, adjustment disorder, and other stress reactions was associated with a 31% increased risk in primary neurodegenerative diseases such as AD and an 80% increased risk in vascular neurodegenerative disease (51). A recent meta-analysis quantifying the association of PTSD and risk of dementia showed that PTSD as a strong risk factor for all-cause dementia in both military and non-military populations (52). In fact the study noted greater increase in dementia risk in the general population. However, the study also acknowledged greater increased risk for dementia in non-US Studies than studies from the US and also in studies with more than 50% females, making it difficult to interpret the difference between the general population and the military in US Veterans.

It is important to note that the prevalence of PTSD is likely greater in the military. Because of improved military health and battlefield survival from acute combat related injuries, veterans are at increased risk of PTSD and other mental health conditions which have been shown to be associated with developing chronic neurodegenerative diseases including AD and other dementias (7, 53). For example, both the National Comorbidity Survey (NCS) and its replication (NCS-R) estimated the lifetime prevalence of PTSD among adult Americans to be 6.8% (3.6%, among men and 9.7% among women) (54). The estimated lifetime prevalence of PTSD among Veterans on the other hand was 30.9% for men and 26.9% for women. 9.3% of Veterans seen in PACT have a diagnosis of PTSD (39). Among recent cohorts of veterans such as those returning from Iraq and Afghanistan, it is estimated that 17% experienced PTSD. Vietnam veterans have been found to have a 20–30% lifetime prevalence of combat-related PTSD. Since PTSD is a chronic condition, appearing in some cases many years after return, it is not surprising that even among World War II veterans persistence of PTSD after 45 years is estimated at least at 12%. One study reported that veterans with an ICD diagnosis of PTSD had cumulative incidence rate of 10.6% for dementia, while those without PTSD had a rate of 6.6% (46). Neither demographic nor medical comorbidities have been shown to modify the impact of PTSD on dementia risk. This result has been replicated in smaller studies examining older

veterans (47), and the effect does not appear to be modified by the use of psychotropic medications (49). Even if the increased risk for dementia is lower in veterans than in the general public these differences in prevalence of PTSD may lead to a greater number of cases.

## POTENTIAL FOR MANAGING RISKS TO COGNITIVE HEALTH

As an integrated health care system, the VHA has opportunities to provide management of health conditions that may reduce the risk of cognitive impairment and dementia. Quality management indicators are powerful tools to encourage facilities to systematically screen for important co-morbidities and to meet certain rates of service delivery. Availability of "wrap around" services can be used to overcome considerable barriers in disease management. Several examples of such programs in the VA include the Self-Management to Prevent (STOP) Stroke Program to help veterans at risk for stroke and stroke recurrence. As a response to patients' initial feedback indicating desire for more in-depth nutrition education in the program, a teleconference program was developed to include the Dietary Approaches to Stop Hypertension (DASH) diet nutrition concepts and transportation services to overcome compliance and retention barriers. Well-developed education and training programs are integrated in clinical practice guidelines and have been used to outreach with health management through community based Veteran Service Groups (VSO) such as American Legion and veteran of Foreign Wars. This is exemplified in POWER (Posts Working for Veterans' Health), an intervention of peer leaders from VSOs designed to improve and facilitate self-care behaviors that contribute to blood pressure control (55). A system wide engagement program in risk reduction is the *MOVE*! Weight-Management Program, which was piloted in 17 VAMCs successfully implemented nationally, with more than 100,000 patients having participated in more than 500,000 visits.

One way to consider risk management is through early detection and screening. While the US Preventive Services Task Force (USPSTF) currently finds inconclusive evidence to recommend routine asymptomatic cognitive screening in the general population (56), it is possible that the high risk for cognitive impairment and dementia in the VA may tilt risk-beneficial ratio in this population to make screening worthy of consideration. In an early study carried out in 7 VA medical centers assessing the feasibility of cognitive screening in older veterans presenting for routine primary care, veterans overwhelmingly accepted cognitive screening administered on the day of a routine primary care clinic visit, with almost 97% agreeing to screening (14). With its experience in comprehensive screening programs including TBI, a risk factor for dementia, the VA has potential in implementing system wide approaches in managing health risks that impact dementia prevention care delivery.

While these studies have focused on translating science to care delivery, none have yet to examine cognitive benefits that might have been gained. In fact, the lower risk of dementia from PTSD among veterans within the VA health care system compared to the general population may partly be the result of availability and of delivery of targeted treatments in the VA for this condition which may not be available to the general public. Transformational care delivery is possible and the opportunity to assess the impact in reduction of cognitive impairment and dementia is within reach.

## CONCLUSIONS

Risk of dementia are high among veterans and are influenced by many factors, including changes in veterans' demographic and socioeconomic characteristics, clinical, health, lifestyle features, and military related risk factors. Compared to those without dementia, veterans with dementia are older, sicker, and more likely to rely on care within and outside the VA. Veterans with dementia who also seek care outside the VA may be particularly vulnerable as multiple sources of care can lead to fragmentation of care that may negatively impact the quality of care veterans receive and their health outcomes.

The comprehensive nature of health care delivery within an integrated system such as the VHA provides opportunities to improve both quality of care and cost effectiveness of care. System wide approaches to screening, behavioral management, and disease prevention have potential to mitigate risks of dementia. Interventions to reduce fragmentation of services and integrate care across settings can improve both quality of care and cost effectiveness. These approaches have had successes with other chronic conditions and research in cognitive health and dementia care delivery may provide similar best practices for aging veterans.

## AUTHOR CONTRIBUTIONS

MS and CZ substantial contributions to conception or design of the work, and acquisition, analysis, interpretation of data for the work, drafting of the work, revising it critically for important intellectual content, final approval of the version to be published, and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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