Abstract—Veterans who have been deployed to combat often have complex medical histories, including some combination of traumatic brain injury (TBI); mental health problems; and other chronic, medically unexplained symptoms (i.e., chronic multisymptom illness [CMI] clusters). How these multiple pathologies relate to functional health is unclear. In the current study, 120 Veterans (across multiple combat cohorts) underwent comprehensive clinical evaluations and completed self-report assessments of mental health symptoms (Patient Health Questionnaire-2 [PHQ-2], Posttraumatic Stress Disorder Checklist–Civilian Version [PCL-C]) and functional health (Veterans RAND 36-Item Health Survey). Canonical correlation and regression modeling using split-sample permutation tests revealed that the PHQ-2/PCL-C composite variable (among TBI severity and number of problematic CMI clusters) was the primary predictor of multiple functional health domains. Two subscales, Bodily Pain and General Health, were associated with multiple predictors (TBI, PHQ-2/PCL-C, and CMI; and PHQ-2/PCL-C and CMI, respectively), demonstrating the multifaceted nature of how distinct medical problems might uniquely and collectively impair aspects of functional health. Apart from these findings, however, TBI and CMI were not predictors of any other aspects of functional health. Taken together, our findings suggest that mental health problems might exert ubiquitous influence over multiple domains of functional health. Thus, screening of mental health problems and education and promotion of mental health resources can be important to the treatment and care of Veterans.

Key words: chronic multisymptom illness, daily functioning, functional health, mental health, posttraumatic stress, quality of life, symptoms, traumatic brain injury, Veterans, war-related illness.

INTRODUCTION

Veterans who have been deployed to combat often exhibit many physical and mental health symptoms as a consequence of their experiences in service. However, how these multiple war-related illnesses affect Veterans’
functional health and health-related quality of life is currently not well understood. The California campus of the War Related Illness and Injury Study Center (WRIISC) at the Department of Veterans Affairs (VA) Palo Alto Health Care System is one of three WRIISC sites nationwide (including East Orange, New Jersey, and Washington, DC) that focus on the postdeployment health concerns of Veterans by providing consultation services as part of a national effort to provide clinical care to Veterans with complex health problems [1].

Some Veteran patients are eligible to be referred to the WRIISC program by their local VA providers to seek a second opinion on their conditions, such as those who have complex health conditions and medically unexplained symptoms, show little to no symptom improvement following several tests and/or treatment or follow-up, or have possible service-related problems or concerns related to environmental exposures. (For referral and enrollment information, see http://www.warrelatedillness.va.gov/WARRELTEDILLNESS/referral/) As such, the WRIISC program evaluates Veterans who served in all combat eras from the Vietnam War to Operation Iraqi Freedom/Operation Enduring Freedom/Operation New Dawn (OIF/OEF/OND). Enrolled Veterans are brought to the designated service-area WRIISC site for a multiday assessment, during which they are evaluated by a specialized team of clinicians, researchers, and educators who offer recommendations for further testing and treatment.

Typical WRIISC patients have a complex medical history with problems related to the chronic sequelae of traumatic brain injury (TBI), mental health disorders (e.g., depression, posttraumatic stress disorder [PTSD]), and other chronic medical conditions that involve multiple symptoms without clear explanations. These chronic, medically unexplained cases span multiple domains (i.e., clusters), including fatigue; pain; problems in pulmonary, dermatologic, and gastrointestinal systems; and problems with sleep, mood, cognition, and memory [2–3]. These cases, collectively described as chronic multisymptom illness (CMI), are frequently observed among Veterans who have served in the Gulf War [4]. However, in more recent reports, CMI-like cases are also described in Veterans deployed to other conflicts (e.g., OIF/OEF/OND) as well as in nondeployed Veterans [5–6].

WRIISC patients are more likely to exhibit TBI, mental health problems, and problems in CMI symptom clusters at higher rates than are epidemiological Veteran samples because patients are referred to the WRIISC program specifically because they presented chronic and complex medical problems. In representative Veteran samples, TBI is observed in an estimated 10 to 30 percent of Veterans [7–8]. Similar proportions are reported for depression (14%; National Alliance on Mental Illness; http://www.nami.org) and PTSD (4–20% in Gulf War-era and OIF/OEF/OND Veteran samples) [9–11]. Estimated numbers of Veterans affected by CMI are more variable because of multiple working case definitions. Nonetheless, an estimated 8 to 62 percent of Gulf War-era Veteran samples are thought to be affected by CMI problems [3–4]. The higher rates of TBI, mental health problems, CMI problems, and comorbidities in WRIISC patients introduce an analytical challenge and potentially obfuscate comparisons with studies involving other Veteran cohorts (e.g., the Vietnam War, Gulf War, and OIF/OEF/OND conflict eras [12–16]). However, such patients provide a unique opportunity to gain insights into the potential effect that multiple medical problems and comorbidities might have on other health outcomes.

Because postdeployed Veterans typically experience some combination of TBI, mental health, and CMI symptoms, a better understanding of how multiple medical factors are potentially associated with impaired functional health and health-related quality of life may inform more effective treatment approaches [16–21]. Whereas contemporary medical practice generally treats individual medical conditions independently from comorbidities, different pathologies can have overlapping or compounding effects. Thus, a more integrated treatment approach addressing multiple aspects of a Veteran’s health might be more beneficial. In the current study, we aimed to characterize the extent to which commonly observed war-related pathologies (i.e., TBI, depression, PTSD, and problems in CMI clusters) were associated with various aspects of functional health and health-related quality of life in Veterans evaluated at the California WRIISC program.

We expected different domains of functional health to be uniquely associated with different medical factors. For example, TBI and problems in CMI symptom clusters were expected to be more strongly associated with physical, bodily, and pain-related impairments (e.g., limited ability in moderate and intense physical activities, difficulty in performing work, limitations as a result of severe pain), whereas mental health symptoms related to depression and PTSD might be more strongly associated with psychological, emotional, and social impairments (e.g., limitations from feeling low energy and anxious, limitations in social activities). However, the relationships between medical factors and functional health
might be substantially more complex, with multiple medical factors (TBI, depression, PTSD, problems in CMI clusters) influencing various aspects of functional health. Thus, the current investigation represented a preliminary effort toward elucidating these relationships in a Veteran sample characterized by multiple comorbid pathologies.

**METHODS**

**Sample**

Participants in this study \((N = 120; \text{mean age, 47.8 yr, range 27–78 yr; 15 females})\) were Veterans seen at the California WRIISC. They are a sample of patients evaluated at the WRIISC program who met the following criteria: (1) completed a self-report questionnaire packet assessing demographic and health-related information, (2) underwent the comprehensive on-site clinical evaluation, and (3) gave written consent to making their data available for research purposes.

The Veterans included in the study were part of a mixed cohort sample, the majority of whom had served in combat. Most Veterans had been deployed to the Gulf War (46%), but a substantial proportion had been deployed to OIF/OEF/OND (38%). Smaller groups were deployed to the Vietnam War (14%) and other conflicts (6%). Fifteen percent have been deployed to multiple combat theaters, and 6 percent have never been deployed. This small number of nondeployed Veterans demonstrates the fact that chronic illnesses and injuries can also be incurred from training-related activities and exposures outside of combat. Although the WRIISC programs typically treat combat Veterans, the programs also receive and enroll referrals involving noncombat Veterans who present persistent complex symptoms. For sample characteristics, see Table 1 and the Figure.

**Clinical Assessments and Determination of Clinical Conditions**

**Neurological Examination for Assessment of Traumatic Brain Injury**

All patients included in the study underwent a complete neurological examination by a neurologist for the assessment of TBI. Each patient was examined and diagnosed Table 1. Complete demographic and medical history information for the Veterans evaluated in the California WRIISC program \((N = 120)\).

**Table 1.**

| Description |
|------------|
| \begin{tabular}{|l|l|}
| Demographic* & Description & \\
| Age, yr (range) & 47.8 (27–78) & \\
| Education, yr (mean ± SD) & 14.3 ± 3.5 & \\
| Sex, Female, % & 12.5 & \\
| Combat History/Theater, % & \\
| Vietnam & 14.2 & \\
| GW1 & 45.8 & \\
| OIF/OEF/OND & 38.3 & \\
| Other & 5.8 & \\
| No. Deployments, % & \\
| 0 & 5.8 & \\
| 1 & 79.2 & \\
| 2+ & 15.0 & \\
| Medical History, % & \\
| TBI Diagnosis† & 57.5 & \\
| None & 42.5 & \\
| Mild & 52.5 & \\
| Moderate/Severe & 5.0 & \\
| Probable Depression‡ & 59.2 & \\
| PTSD Diagnosis§ & 65.0 & \\
| Affected CMI Clusters, %§ & \\
| Pain & 95.8 & \\
| Sleep & 85.8 & \\
| Gastrointestinal & 60.0 & \\
| Cognitive NOS & 55.8 & \\
| Fatigue & 49.2 & \\
| Dermatologic & 34.3 & \\
| Pulmonary & 24.2 & \\
| Problematic CMI Clusters, No. (cumulative %) & \\
| 0 & 3.3 (100.0) & \\
| 1 & 1.7 (96.7) & \\
| 2 & 5.0 (95.0) & \\
| 3 & 23.3 (90.0) & \\
| 4 & 29.2 (66.7) & \\
| 5 & 21.7 (37.5) & \\
| 6 & 12.5 (15.8) & \\
| 7 & 3.3 (3.3) & \\
\end{tabular} |

*Demographic and combat history information were collected from Veterans during intake into the California WRIISC program.
†Diagnoses of TBI and PTSD were made by the staff neurologist, clinical psychologist, and psychiatrist.
‡Likelihood of depression was based on the self-report screening measurement Patient Health Questionnaire-2, using a cutoff of 3.
§Diagnoses of problems in CMI symptom clusters were made by providers at other various specialty clinics.

CMI = chronic multisymptom illness, GW1 = Gulf War 1, No. = number, NOS = not otherwise specified, OEF = Operation Enduring Freedom, OIF = Operation Iraqi Freedom, OND = Operation New Dawn, PTSD = posttraumatic stress disorder, SD = standard deviation, TBI = traumatic brain injury, WRIISC = War Related Illness and Injury Study Center.
decreased level of consciousness, any loss of memory immediately prior to or following injury, any alteration in mental state (e.g., confusion, disorientation, slowed thinking), neurological deficits (e.g., weakness, loss of balance, loss in vision or other senses, aphasia), or intracranial lesion as the result of an external force. Although Veterans may have possibly (or even likely) sustained multiple TBIs in the past, the neurologist made all diagnoses based on one self-reported incident at the patient's disclosure. Accurate and reliable diagnosis of TBI was limited because it relied on self-reporting without consistently available supporting documentation or medical information at the time of injury. However, self-reporting and sparse medical records were the only information sources available [24]. Based on the retrospective self-report (corroborated with a chart review of past medical records in the VA's centralized charting system prior to the interview), patients were diagnosed as having no TBI, mild TBI (normal brain scan, loss of consciousness <30 min, altered mental state <24 h, posttraumatic amnesia <1 d), or moderate-severe TBI (normal or abnormal brain scan, loss of consciousness >30 min, altered mental state >24 h, posttraumatic amnesia >1 d).
Assessment of Chronic Multisymptom Illness

Veterans’ CMI symptom profiles were characterized by noting active problems within individual CMI clusters. A chart review of patients’ on-site evaluations was performed via the VA’s Computerized Patient Record System, and current diagnoses in the following clusters were noted: pain, fatigue, dermatologic, gastrointestinal, pulmonary, sleep, and cognitive disorders not otherwise specified. Only diagnoses charted during the patients’ WRIISC evaluations were included in this study. A CMI symptom cluster was considered problematic if one or more medical conditions within the cluster were noted by a provider. Cognitive disorders not otherwise specified were diagnosed by consensus of the psychiatrist, neurologist, and clinical psychologist. The total number of unique problematic CMI clusters was tallied for each patient.

Self-Report Measures

Probable Depression

Patients completed the Patient Health Questionnaire-2 (PHQ-2), a brief, two-item measure that screens for symptoms of depression. It was shown to have acceptable sensitivity (83%–100%) and specificity (77%–92%) for major depression in civilian and Veteran samples and is routinely used in the VA as part of the Primary Care Manual [25–27].

Posttraumatic Stress

Patients completed the PTSD Checklist–Civilian Version (PCL-C), a 17-item self-report measure that assesses severity of symptoms resulting from stressful life experiences (not restricted to military-specific trauma) across different symptom domains of PTSD (re-experiencing, avoidance, and hyper arousal; criteria from the Diagnostic and Statistical Manual of Mental Disorders-4th Edition) [28–29]. The sum of all 17 responses was used as an indicator of global PTSD symptom severity. Psychometric properties of the PCL-C have been reported as favorable, with good test-retest reliability (>0.75), internal consistency (>0.83), and strong correlation with clinical standards [29–30].

Functional Health Outcomes

The Veterans RAND 36-Item Health Survey (VR-36) was administered to assess constructs affecting health-related quality of life. The VR-36 is a 36-item, Veteran-specific inventory based on the functional health measure 36-Item Short Form Survey [31–33]. The VR-36 assesses different aspects of functioning and well-being across eight subscales (domains): Physical Functioning, Role Limitations: Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Limitations: Emotional, and Mental Health. Descriptions and sample items of each subscale are presented in Table 2. These Likert-style items were computed into summary scores for each domain (scaled 0–100), with greater scores indicating better functioning. Internal reliability is generally good, with seven of the eight individual domains having Cronbach alpha between 0.76 and 0.91 [34].

Predictors of Functional Health Outcomes

To quantify the associations between medical factors (TBI severity, PHQ-2, PCL-C, and number of problematic CMI clusters) and functional health measures (the eight VR-36 subscales), we performed primary analyses to observe the overall multivariate relationship between medical factors and functional health measures, followed by confirmatory regression modeling and cross-validation using split-sample permutation tests.

Data Transformation

Prior to data analyses, we inspected all self-report measures for outliers. Outlier detection was performed using the Tukey procedure on the PHQ-2, PCL-C, and VR-36. Outliers were defined as >1.5 times the interquartile range beyond the first and third quartiles. No outliers were identified based on the PHQ-2 and PCL-C, but four patients were flagged as potential outliers among the eight VR-36 subscales. On further inspection, however, we found that distributions of many of the VR-36 subscales were positively skewed (overall tendency to report lower scores on nearly all subscales; Table 2. Because our sample was expected to exhibit greater disability in functional health, rather than exclude the flagged patients with lower subscale scores as outliers, we transformed all VR-36 subscales scores using Box-Cox transformations to give each subscale a more normal distribution.

In addition, because we expected depression and PTSD to be correlated, we combined the PHQ-2 and PCL-C scores to form a mental health composite (by summing the Z-transforms of the two) [35–36]. Inclusion of collinear terms in regression modeling would have negatively influenced interpretation of results and reduced statistical power. Thus, although we were unable to distinguish the relative contributions of depression and PTSD symptoms
Table 2.
Descriptions of self-report measures an overall sample mean ± standard deviation (n = 120).

| Measurement   | Description                                                                 | Sample Items                                                                 | Mean ± Standard Deviation |
|---------------|-----------------------------------------------------------------------------|------------------------------------------------------------------------------|--------------------------|
| PHQ-2 (2 items) | Frequency of depressed mood and anhedonia over the past 2 wk                 | Little interest or pleasure in doing things?                                | 3.2 ± 2.1                |
| PCL-C (17 items) | DSM-IV symptoms of PTSD                                                     | Repeated, disturbing memories, thoughts, or images of a stressful experience from the past? | 52.5 ± 17.9             |
| VR-36         | Health-related quality of life, disease burden, and effect on daily functioning |                                                                              | —                        |
| Physical Functioning (9 items) | Limitations in range of physical activities | Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf? | 41.7 ± 26.4             |
| Role Limitations: Physical (5 items) | Limitations in performing daily activities because of physical problems | Had difficulty performing the work or other activities (for example, it took extra effort)? | 24.9 ± 25.7             |
| Bodily Pain (2 items) | Intensity of pain and extent to which pain interferes with daily activities | During the past 4 wk, how much did pain interfere with your normal work (including both work outside the home and housework)? | 26.3 ± 22.9             |
| General Health (4 items) | Perception of general health | In general, would you say your health is [poor–excellent]? Compared to one year ago, how would you rate your health in general now? | 29.1 ± 19.0             |
| Vitality (4 items) | Subjective rating of energy and fatigue | Did you have a lot of energy? Did you feel worn out? | 20.3 ± 19.9             |
| Social Functioning (1 item) | Limitations in social activities | During the past 4 wk, to what extent have your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups? | 26.6 ± 22.9             |
| Role Limitations: Emotional (3 items) | Limitations in performing daily activities due to emotional problems | Didn’t do work or other activities as carefully as usual? Accomplished less than you would like? | 48.8 ± 33.5             |
| Mental Health (5 items) | Subjective rating of mental health and emotional well-being | Have you been a very nervous person? Have you felt so down in the dumps that nothing could cheer you up? | 47.9 ± 24.6             |

Note: Raw VR-36 scores are described prior to Box-Cox transformation.

DSM–IV = Diagnostic and Statistical Manual of Mental Disorders-4th Edition, PCL-C = Posttraumatic Stress Disorder Checklist–Civilian Version, PHQ-2 = Patient Health Questionnaire-2, PTSD = posttraumatic stress disorder, VR-36 = Veterans RAND 36-Item Health Survey.

To functional health, the use of a PHQ-2/PCL-C composite variable allowed us to investigate the potential effects of a broader mental health construct.

**Primary Analyses**

Our primary objective was to describe potential relationships between medical factors and multiple functional health domains, so we performed a series of multivariate and multiple regression analyses.

**Canonical correlation analysis.** To gain an appreciation of the overall relationship between medical factors and functional health measures, we performed a canonical correlation analysis with TBI severity, PHQ-2/PCL-C composite, and number of problematic CMI clusters as predictor variables, and the eight subscales of the VR-36 as outcome variables.
**Split-sample permutation testing and cross-validation of multiple regression models.** To quantify specific associations between medical factors and functional health measures (especially those indicated by the canonical correlation analysis), we tested standard regression models using split-sample permutation tests and cross-validation. Permutation tests using split samples offered several analytic advantages: precise estimates of effect sizes and interquartile ranges, insights into the overall distributions of effects, and metrics of generalizability based on cross-validations between the tested (discovery) and withheld (generalizability) subsamples.

The sample of 120 subjects was split into two randomly selected groups of 60 across 10,000 iterations. During each iterative process, for each VR-36 subscale, a standard linear regression model with medical factors and demographic variables (age and education) as predictor variables and the VR-36 subscale scores as the outcome variables was tested using the discovery subsample. Regression coefficients from the discovery model were then applied to the generalizability subsample data to obtain predicted VR-36 subscale scores. Cross-validation reliability was quantified as a Pearson correlation between the predicted and actual subscale scores in the generalizability subsample. After 10,000 iterations, distributions of the overall model fit (adjusted $R^2$) and its cross-validation ($R$) were obtained for each VR-36 subscale.

**Contribution of individual medical factors to functional outcomes.** Using permutation tests, we also computed distributions of estimated effect sizes (beta, $t$-statistic) for each regression coefficient (i.e., for each medical factor, accounting for age and education as covariates), for each VR-36 subscale. By examining these distributions, we inferred the relative importance of each medical factor to each functional health domain.

**Secondary Analyses**

The medical factor variables in the primary analyses varied in form, so we ruled out potential effects of variable structure on the medical factor/functional outcome relationships by performing the same analyses on binary forms of the medical factor variables. Medical factors were binarized as follows: TBI severity (no TBI versus mild TBI; moderate-severe TBI cases were excluded from this analysis because of potential construct heterogeneity if combined with mild TBI cases), PHQ-2 (using a cutoff of 3+), PCL-C (using a cutoff of 55+), and CMI variables (using a median split of 4+ symptom clusters) [25,27,37–38]. The cutoff points for the PHQ-2 and PCL-C were chosen because the WRIISC Veteran sample had more complex medical histories than those reported in typical Veteran samples.

We also performed post hoc zero-order correlation analyses between each medical factor and each VR-36 subscale to observe relative associations without regressing out the potential influences of the other medical factors or demographic variables.

Although we considered depression and PTSD symptoms jointly in the primary analyses because of potential collinearity issues, we also carried out the same canonical correlation and split-sample permutation modeling analyses while considering PHQ-2 and PCL-C independently.

We had hoped to gain a more nuanced understanding of potential medical factor/functional health domain relationships through these secondary analyses, but because these analyses are exploratory we have refrained from discussing them in detail in this article.

**RESULTS**

**Medical History and Self-Report Measures**

More than half of California WRIISC Veterans met diagnostic criteria for mild (52.5%) or moderate TBI (5%). An even larger proportion met diagnostic criteria for PTSD (65%). Nearly all (97%) reported problems from at least one CMI symptom cluster; two-thirds had problems in four or more unique CMI symptom clusters. Complete demographic and medical history information are shown in Table 1.

Mean response on the PHQ-2 was 3.2, and the mean response on the PCL-C was 52.5. Mean raw scores on VR-36 subscales ranged from 20.3 to 48.8. Descriptive data for all self-report measures are shown in Table 2.

**Primary Analyses**

**Canonical Correlation Analysis Results**

A significant relationship was observed between the first canonical variate pair (Wilks lambda = 0.24, $F = 8.43$, $p < 0.001$). The pooled squared canonical correlation for the first canonical pair was 0.88. In the first canonical root, the PHQ-2/PCL-C composite was the most important (standardized canonical coefficient = 0.53) among predictor variables, and Mental Health (standardized canonical coefficient = −0.61), Role Limitations: Emotional (stan-
standardized canonical coefficient = −0.37), and Social Functioning (standardized canonical coefficient = −0.20) were the most important among outcome variables. All canonical correlation results are presented in Table 3.

Split-Sample Permutation Tests and Cross-Validation

Split-sample permutation tests of regression models predicting VR-36 subscale scores indicated that the Mental Health, Role Limitations: Emotional, and Social Functioning subscales were substantially accounted for by the medical factors and covariates (mean adjusted $R^2 = 0.61, 0.52, 0.26$, respectively). The Bodily Pain, Vitality, and General Health subscales were also well modeled by medical factors and covariates to lesser extents (mean adjusted $R^2 = 0.19, 0.14, 0.13$, respectively). The Physical Functioning and Role Limitations: Physical subscales were not well explained by the medical factors included in the analyses. All split-sample permutation test results and 95 percent interquartile ranges are shown in Table 4.

The Mental Health, Role Limitations: Emotional, and Social Functioning subscales also had the highest cross-validation reliability (adjusted mean $R = 0.78, 0.71, 0.48$, respectively). The Bodily Pain, Vitality, General Health, and Physical Functioning subscales had slightly lower cross-validation reliability (mean adjusted $R = 0.40, 0.31, 0.30, 0.25$, respectively). Only the Role Limitations: Physical subscale had cross-validation reliability close to zero. All cross-validation results and 95 percent interquartile ranges are shown in Table 4.

Table 3.

| Variables | Canonical Roots |
|-----------|-----------------|
|           | 1               | 2               | 3               |
| Independent |                 |                 |                 |
| TBI Severity | 0.016           | 0.772           | −0.675          |
| PHQ-2/PCL-C Composite* | 0.533           | −0.173          | −0.014          |
| No. CMI Clusters | 0.069           | 0.611           | 0.808           |
| Dependent   |                 |                 |                 |
| Physical Functioning | −0.070         | 0.007           | 0.445           |
| Mental Health† | −0.607         | 0.356           | 0.229           |
| Vitality    | 0.018           | 0.377           | −0.098          |
| Social Functioning† | −0.203         | 0.064           | −0.889          |
| Bodily Pain | −0.031          | −1.150          | 0.342           |
| General Health | 0.014           | −0.426          | −0.749          |
| Role Limitations: Physical | 0.143           | 0.285           | 0.234           |
| Role Limitations: Emotional† | −0.369         | 0.087           | 0.353           |
| $R$         | 0.846           | 0.349           | 0.204           |
| Wilks Lambda | 0.238           | 0.842           | 0.958           |
| $F$         | 8.435           | 1.414           | 0.806           |
| $p$         | <0.001          | 0.145           | 0.526           |
| $df1$       | 24.000          | 16.000          | 6.000           |
| $df2$       | 316.730         | 220.000         | 111.000         |

Table 3.

Canonical correlation results. In bold: significant canonical pairs ($p < 0.05$).

*The most important among independent variables.
†The most important among dependent variables.
CMI = chronic multisystem illness, No. = number, PHQ-2/PCL-C = Patient Health Questionnaire-2/Posttraumatic Stress Disorder Checklist–Civilian Version, TBI = traumatic brain injury.

Secondary Analyses

Secondary analyses assessing potential effects of variable structure and zero-order correlations were largely similar to the findings described previously.
Table 4.
Results of standard multiple regression models quantifying associations between medical factors and functional health outcomes. In bold: 95 percent interquartile ranges (IQRs) that do not span zero for both overall model fit and cross-validation performance and corresponding columns.

| Functional Health Outcomes | Overall Model Fit (Adjusted $R^2$) | 95% IQR | Cross-Validation Performance ($R$) | 95% IQR |
|-----------------------------|-----------------------------------|---------|-----------------------------------|---------|
| Mental Health               | 0.612                             | 0.474 to 0.737 | 0.775 | 0.692 to 0.852 |
| Role Limitations: Emotional | 0.524                             | 0.402 to 0.640 | 0.708 | 0.619 to 0.786 |
| Social Functioning          | 0.257                             | 0.110 to 0.423 | 0.479 | 0.330 to 0.607 |
| Bodily Pain                 | 0.188                             | 0.047 to 0.351 | 0.402 | 0.244 to 0.545 |
| Vitality                    | 0.138                             | 0.003 to 0.306 | 0.311 | 0.133 to 0.475 |
| General Health              | 0.128                             | 0.001 to 0.268 | 0.303 | 0.126 to 0.456 |
| Physical Functioning        | 0.089                             | −0.027 to 0.237 | 0.250 | 0.063 to 0.409 |
| Role Limitations: Physical  | 0.026                             | −0.065 to 0.162 | 0.105 | −0.105 to 0.279 |

Note: Permutation tests were performed based on $N = 120$ patients split into two groups, discovery ($n = 60$) and generalizability ($n = 60$), over 10,000 iterations.

Table 5.
Effect of individual medical factors on functional health outcomes ($t$-statistic and 95% interquartile range [IQR]). In bold: 95 percent IQRs that do not span zero and corresponding columns.

| Medical Factors       | TBI Severity | 95% IQR       | PHQ-2/PCL-C Composite | 95% IQR       | No. CMI | 95% IQR       |
|-----------------------|--------------|---------------|-----------------------|---------------|---------|---------------|
| Mental Health         | 0.263        | −1.063 to 1.678 | −9.171 −12.093 to −6.797 | −0.275 −1.569 to 1.063 |         |
| Role Limitations: Emotional | −0.451   | −1.976 to 1.007 | −7.581 −9.619 to −5.817 | −0.377 −1.794 to 0.981 |         |
| Social Functioning    | 0.076        | −1.286 to 1.461 | −4.065 −5.976 to −2.410 | −1.248 −2.627 to 0.127 |         |
| Bodily Pain           | −1.903       | −3.422 to −0.497 | −2.196 −3.775 to −0.756 | −1.412 −2.811 to −0.047 |         |
| Vitality              | 0.243        | −1.142 to 1.608 | −2.914 −4.634 to −1.412 | −0.455 −1.872 to 0.945 |         |
| General Health        | −0.143       | −1.645 to 1.317 | −2.490 −4.175 to −0.870 | −1.502 −2.929 to −0.117 |         |
| Physical Functioning  | −0.780       | −2.120 to 0.483 | −2.204 −3.752 to −0.738 | −0.558 −2.097 to 0.970 |         |
| Role Limitations: Physical | −0.305   | −1.798 to 1.142 | −1.620 −3.284 to −0.082 | −0.352 −1.674 to 0.983 |         |

Note: Results of standard multiple regression models quantifying the associations between medical (TBI severity, PHQ-2/PCL-C composite, and number of problematic CMI clusters) and demographic factors (age, years of education) and various daily function domains. Effects of individual medical factors (TBI severity, PHQ-2/PCL-C composite, number of problematic CMI clusters) are shown, accounted for demographic factors (age and education) and all other medical factors. Permutation tests were performed based on $N = 120$ patients split into two groups, discovery ($n = 60$) and generalizability ($n = 60$), over 10,000 iterations.

CMI = chronic multisymptom illness, No. = number, PHQ-2/PCL-C = Patient Health Questionnaire-2/Posttraumatic Stress Disorder Checklist–Civilian Version, TBI = traumatic brain injury.

DISCUSSION

The current investigation considered whether and to what extent war-related illnesses such as TBI, mental health problems, and problems in CMI clusters are associated with multiple domains of functional health/health-related quality of life in a non-cohort-specific Veteran sample marked by complex medical comorbidities. Converging results from canonical correlation and split-sample permutation regression modeling indicate that such medical factors seem to affect a broad range of functional health, with impairments spanning psychological, mood/affect, social, and bodily domains. These findings support and complement previously reported associations between TBI, depression, PTSD, and problems in CMI clusters and functional health outcomes in Gulf War and OIF/OEF Veterans [15,18,39].

For the vast majority of functional health domains, the Mental Health construct captured by the PHQ-2/PCL-C composite variable is the only strong indicator. These findings are consistent with previous reports and confirm the expected relationship between mental health symptoms and psychological, mood/affect, and social aspects of health-related quality of life [13,40–41].

The Bodily Pain subscale, which indexes functional limitations because of physical pain, is strongly associated with TBI severity and number of problematic CMI clusters in addition to PHQ-2/PCL-C. Given the great likelihood of Veterans suffering co-occurring injuries during combat (e.g., co-occurring PTSD following TBI...
or other bodily injuries), the observation that physical and psychological sources of trauma might jointly manifest as a common form of functional limitation is not surprising. This finding also aligns with previous reports linking TBI, mental health problems, and CMI problems to functional limitations from pain [15,42]. In addition, this finding also demonstrates the multifaceted nature of how distinct medical problems might uniquely and collectively impair specific aspects of functional health.

Similarly, the General Health subscale, which indexes general perceptions and attitudes toward one’s health, is strongly associated with both PHQ-2/PCL-C and the number of problematic CMI clusters. This finding is consistent with previous reports and highlights the complementary influences of mental health and physical medical symptoms affecting Veterans’ general views toward health and quality of life [13–14,39].

We did not observe associations between TBI severity and seven of the eight VR-36 subscales. This result is somewhat unexpected in light of previous studies involving civilian and OIF/OEF/OND Veteran samples [15,43–44]. Similarly, the lack of associations between CMI status and six of the eight subscales is also surprising given the previously described associations, particularly from Gulf War and general Veteran samples [4,31,45]. One explanation for these discrepancies is that the inclusion of mental health variables in the current analyses potentially obscures precise characterizations of the associations between TBI and CMI and functional health measures. Previous studies have suggested that mental health factors in general, and PTSD in particular, might be a mediator of such relationships [13,15,46–47]. However, post hoc zero-order correlation analyses also fail to show any relationships between TBI/CMI and functional health (with one exception being a small association between TBI severity and the Role Limitations: Emotional subscale). A more likely possibility is that the symptoms and problematic features in TBI and CMI are too specific (e.g., involving memory, cognition, somatic problems) and their operationalization in the current study is too crude, such that their potential relationships with functional health domains are not aptly measured. Indeed, previous studies reporting such associations tend to have larger samples and adopt between-groups study designs that aim to minimize within-group heterogeneity. Also plausible, however, is the idea that physical medical problems such as those stemming from TBI and problems in CMI symptom clusters might simply not be very strong indicators of daily functioning compared to mental health problems. This explanation might be particularly pertinent in a patient sample with psychiatric comorbidities.

Although previous studies have reported associations between different forms of war-related pathologies, we did not observe overwhelming associations between TBI, mental health symptoms, and problems in CMI symptom clusters. Apart from the expected associations between PTSD and depression and between TBI and PTSD, no other associations among medical factors were observed [15–16,19,35–36,48–50]. This result is surprising given the body of Gulf War and OIF/OEF/OND cohort research that shows associations between TBI and CMI and mental health conditions and CMI [17–18,21,51–54]. These discrepancies might result from the differences in variable definition, analytic decision, sample size, or some combination of all of these. On the other hand, the association between TBI and PTSD juxtaposed to the lack of associations between them and CMI problems indicates that the traumatic events and experiences leading to development of TBI and PTSD are likely to be qualitatively similar but distinct from those that cause chronic, medically unexplained symptoms in CMI clusters (e.g., related to exposure to a combination of environmental, biological, and chemical agents) [55–57].

The complex medical problems and high comorbidity rates of California WRIISC Veterans introduce potential limitations on both analytical and inferential fronts. Incidences of TBI, probable depression, PTSD, and problems in CMI clusters are higher in California WRIISC patients than in other epidemiological Veteran samples across multiple conflict eras, limiting comparisons with other studies.

Apart from the complexities introduced by our unique Veteran patient sample, other factors might also limit the inferential power of our findings. In particular, we adopt an integrative approach that brings together a range of clinically derived and self-reported data, which might present analytic challenges.

The clinically derived information (diagnoses of TBI and CMI cluster problems) is somewhat hindering because of its binary and nonparametric nature. As such, we are unable to gain fine-grained insights regarding the severity of patients’ clinical status. This limitation stifles our otherwise powerful analytic strategy. In particular, a more thorough documentation of the chronic sequelae of TBI will be more informative. On the other hand, our self-report measures (PHQ-2, PCL-C, VR-36), although more continuous are subject to response bias, response
compliance, and deviant responding concerns inherent to self-report instruments.

The split-sample permutation analytic approach with cross-validation, though offering several advantages, is correlational and does not allow causal inferences to be made. Even in the event of very strong associations, the potential causal directionality of such associations cannot be known with certainty without additional longitudinal and intervention research methods. For example, although individuals characterized as having high negative affect are thought to endorse medical symptoms at a higher rate, an equally plausible interpretation is that individuals with more medical symptoms might experience heightened negative affect. Both explanations can be true, and the overall relationship between negative affect and medical pathologies is thought to be bidirectional [58–60].

The context within which the data were collected should also be considered. All clinically derived and self-report data were collected as part of the intake and evaluation process during a multiday clinical visit. The quality of the data was susceptible to patient compliance, patient fatigue, disease burden, and the potential for seeking secondary gains [61]. Without consistent and systematic assessments for effort, fatigue, and compliance, we cannot rule out their potential influences on the data.

CONCLUSIONS

Taken together, our results show that in a Veteran sample characterized by complex medical and psychological problems and multiple comorbidities, mental health symptoms related to depression and PTSD emerge as the prominent factor contributing to impaired health-related quality of life. The strong associations between mental health symptom severity and multiple functional health domains suggest that a stronger emphasis on mental health screening, education, and treatment could lead to improvements in health-related quality of life.

Surprisingly, severity of TBI and number of problematic CMI symptom clusters are not identified as overwhelmingly strong indicators of most aspects of functional health. Even so, TBI and CMI cluster symptoms should not be discounted; they are likely to contribute to other aspects of functional health and quality of life beyond the scope of the current investigation.

Improvements in the definition and operationalization of symptoms related to TBI and CMI problems may yield important clinical and analytical value. For example, more continuous and sensitive descriptions of TBI and CMI symptoms with a broader range (or multiple dimensions) of severity stratifications will yield more desirable clinical and analytical properties. Improved clinical and research descriptions that embody more specific details of a given pathology (rather than the simple binary case/control distinctions often made in clinical research) will undoubtedly be more sensitive and lead to more insightful research discoveries.

The current report should be considered a preliminary attempt to characterize the relative contributions of multiple medical and psychological pathologies to health-related quality of life in a non–cohort-specific sample of postdeployed Veterans with complex medical conditions. Future research that considers a broader range of functional health and quality of life indices in a larger sample (and perhaps with a longitudinal design) will be invaluable in illuminating the potential influences that war-related pathologies such as depression, PTSD, TBI, and CMI cluster problems have on Veterans’ livelihood and inform better treatment approaches.

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