Alcohol Use and Substance Use Disorders in Gulf War, Afghanistan, and Iraq War Veterans Compared With Nondeployed Military Personnel

Helen Louise Kelsall*, Millawage Supun Dilara Wijesinghe, Mark Christopher Creamer, Dean Philip McKenzie, Andrew Benjamin Forbes, Matthew James Page, and Malcolm Ross Sim

*Correspondence to Dr. Helen Louise Kelsall, Monash Centre for Occupational and Environmental Health, Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, The Alfred Centre, Commercial Road, Melbourne, VIC 3004, Australia (e-mail: helen.kelsall@monash.edu).

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Although recent veterans have been found to be at increased risk of psychiatric disorders, limited research has focused on alcohol or substance use disorders. This systematic review and meta-analysis examined whether alcohol or substance use disorders were more common in Gulf War, Afghanistan, and Iraq War veterans compared with military comparison groups nondeployed to the corresponding conflict, including never deployed personnel. Literature was searched (1990–2014) in multiple electronic databases. Studies were assessed for eligibility and quality, including risk of bias. Eighteen studies (1997–2014) met inclusion criteria. Pooled analysis based on a random-effects model yielded a summary odds ratio of 1.33 (95% confidence interval (CI): 1.22, 1.46) for alcohol (7 studies) and 2.13 (95% CI: 0.96, 4.72) for substance use (3 studies) disorders among Gulf War veterans, as well as 1.36 (95% CI: 1.11, 1.66) for alcohol (7 studies) and 1.14 (95% CI: 1.04, 1.25) for substance use (4 studies) disorders among Iraq/Afghanistan veterans; meta-regressions found no statistically significant association between theater of war and alcohol use or substance use disorders. Our findings indicate that Gulf and Iraq/Afghanistan war veterans are at higher alcohol use disorder risk than nondeployed veterans, but further studies with increased power are needed to assess substance use disorder risk in Gulf War veteran populations.

Afghan Campaign; alcohol-related disorders; Gulf War; Iraq War; meta-analysis; review; substance-related disorders; veterans’ health

Abbreviations: CI, confidence interval; CIDI, Composite International Diagnostic Interview; OR, odds ratio.

INTRODUCTION

War veterans are susceptible to various psychological illnesses postdeployment because of exposure to war itself and a variety of other possible risk factors related to combat experience (1, 2). Risk factors include the degree of combat exposure, deployment stressors, status of deployed troops (regular, reservists), traumatic brain injury, and factors related to leadership, unit cohesion, and organizational commitment (3).

In the 1990–1991 Gulf War, a large multinational force was deployed to the Gulf area in response to the invasion of Kuwait by Iraq on August 2, 1990. In October 2001 in response to the September 11 attacks on the United States, the United States supported by the United Kingdom, Australia, Canada, France, Germany, and other nations began an invasion of Afghanistan (Operation Enduring Freedom). In March 2003, the Iraq War began (Operation Iraqi Freedom) when a combined force from the United States, United Kingdom, Australia, and Poland invaded Iraq. All US forces withdrew from Iraq by December 2011. Studies of the relationship between deployment to the Gulf War and to Iraq/Afghanistan and health outcomes suggest that veterans of these wars are at increased risk of psychological illnesses compared with personnel not deployed to these conflicts (4–9). However, most research in this field has focused on post-traumatic stress disorder and other anxiety or affective disorders with little emphasis on substance use disorders (10), yet alcohol and other substance use disorders have also long been associated with combat experience in other theaters of war (11–13). The prevalence of heavy drinking and binge drinking has increased in US active duty military personnel between 1998 and 2008 (14), and the alcohol-related serious consequences increased with the intensity of drinking from 4% for non–binge drinkers and 9% for binge drinkers to 19% for heavy drinkers (14).
Personnel with high combat exposure were at increased risk of binge and heavy drinking. These prevalence estimates give some indication of the problem among military personnel.

Over the past decade, systematic reviews have been published concerning various aspects of the health of Gulf War veterans (10, 15–18). However, except for a review by Stimpson et al. (10) in 2003 (covering literature from 1990 to May 2001) of psychiatric disorders in Gulf War veterans, the focus of attention has been mainly on health outcomes other than alcohol or substance use disorders, and even in that review Stimpson et al. (10) in 2003 (covering literature from 1990 to May 2001) of psychiatric disorders in Gulf War veterans, the focus of attention has been mainly on health outcomes other than alcohol or substance use disorders, and even in that review Stimpson et al. (10) reported that there was insufficient evidence available concerning alcohol use disorders to make meaningful conclusions. In the 12 years since the review by Stimpson et al. (10), several new studies have been published on alcohol and other substance use disorders in Gulf War veterans including the Australian Gulf War veteran cohort, a population not included in the above review (19–22). Furthermore, research has been published on the psychological health of veterans of contemporary conflicts in Iraq and Afghanistan, including the occurrence of alcohol use disorders and substance use disorders. Such findings provide further rationale for summarizing the evidence on alcohol and substance use disorders in Gulf War and Iraq War/Afghanistan veterans, in order that clinicians and policymakers may be aware of these issues when managing veterans’ health.

Our systematic review aims to quantitatively review the literature on alcohol and other substance use disorders in Gulf War and Iraq War and/or Afghanistan veterans compared with nondeployed military personnel. It further aims to conduct meta-analyses to assess 1) the odds of experiencing alcohol use disorders, 2) the odds of experiencing other substance use disorders such as illicit drugs (herein termed substance use disorders for brevity), and 3) the odds of any type of substance use disorder combined, compared with nondeployed military personnel.

METHODS

Search strategy

We reviewed the literature for published and unpublished citations from January 1, 1990, to January 24, 2014. Citations were searched by using the multiple electronic databases MEDLINE, MEDLINE In-Process, PsycINFO, Embase, Published International Literature on Traumatic Stress (PILOTS), and the Cochrane Library. Studies that matched the following criteria were included:

1. The study population consisted of military personnel deployed to the Gulf War (1990–1991), Afghanistan (2001–), or the Iraq War (2003–2011) encompassing the Navy, Army, Air Force, Marines, and Coast Guard; medical personnel; and reservists/National Guard;
2. Studies were published in English;
3. The outcome of interest was alcohol use disorders, substance use disorders (e.g., opioids, sedatives, hypnotics, anxiolytics, nicotine, cocaine, cannabis), and (combined) any substance use disorder;
4. The study included a military comparison group that differed in its level of deployment exposure to the coresponding conflict (nondeployed personnel) were defined as personnel who did not serve in the primary area of conflict as per previous systematic reviews (18), and other conflict/other deployed personnel were defined as personnel deployed outside the primary area of conflict or to other conflicts (e.g., Germany, Bosnia); and
5. The study provided enough information to generate an odds ratio by deployment.

Studies of the following type were excluded from the review:

1. The conflict deployed sample was of nonmilitary personnel;
2. Studies that were published in a language other than English;
3. The sample was based on clinical or injured or treatment/help-seeking populations (including studies based on data from Veterans Affairs (VA) treatment facilities); and
4. Studies with no eligible military comparison group (e.g., civilians were used as a comparison group).

We developed a list of free text and Medical Subject Headings terms based on the 3 components in the research question. The components were “A1: Gulf War, Afghanistan War, and Iraq War”; “A2: military personnel, military veterans, military medicine, and veterans’ health”; and “B: psychological disorders.” The final search strategy was as follows: (A1 or A2) AND (B). Key words were customized to each individual database. A modified portion of the search string that was used for the MEDLINE database follows:


The definition of the term veteran varies from country to country. For example, the US definition is of a person who served in the active military naval or air service and who was discharged or released under honorable conditions; the Australian definition is of a person who is taken to have rendered eligible war service; a veteran of the British Armed Forces is defined as any person of any age who has served in the armed forces and generally refers to formerly serving personnel. In this review and meta-analysis, our prime comparison relates to military personnel who deployed to the Gulf War (1990–1991), Afghanistan (2001–), or the Iraq War (2003–2011), that is, veterans of the deployment compared with a military comparison group that differed in its level of deployment exposure to the corresponding conflict, as defined above.
### Table 1. Study Population, Methods, and Main Results in Evaluation of Alcohol/Substance Use Disorders in Gulf War Veterans and Nondeployed Military Personnel

<table>
<thead>
<tr>
<th>First Author, Year (Reference No.)</th>
<th>Study Design</th>
<th>Study Date</th>
<th>Location</th>
<th>Sample</th>
<th>No.</th>
<th>Measure/Definition</th>
<th>Participation</th>
<th>Assessment Risk of Bias</th>
<th>Overall Risk of Bias</th>
<th>Prevalence in GWVs, %</th>
<th>Prevalence in Comparison Group, %</th>
<th>Association Estimate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iowa Persian Gulf Study Group, 1997 (7)</td>
<td>Cross-sectional telephone interview</td>
<td>1997</td>
<td>Iowa, United States</td>
<td>Random sample of regular military and NG/reserve GWVs, and active duty or activated nondeployed personnel stratified by service, age, sex, rank, and ethnicity</td>
<td>1,896 reserves and NG/reserve GWVs; 1,799 active duty or activated nondeployed; female %: GWVs, 61% ; non-GWVs, 58</td>
<td>CAGE-assessed symptoms of alcohol abuse</td>
<td>78% of GWVs and 73% of non-GWVs</td>
<td>Nonresponse bias assessed for demographics; significant differences between responders and nonresponders</td>
<td>Low</td>
<td>17.0</td>
<td>12.2</td>
<td></td>
<td>0.4, 4.5</td>
</tr>
<tr>
<td>Goss Gilroy, Inc., 1998 (6)</td>
<td>Cross-sectional postal survey</td>
<td>1997</td>
<td>Canada</td>
<td>Canadian GWVs (sea, land, air service) invited, Canadian forces sample eligible for active duty but not deployed; matched on gender, age, regular military reserve status</td>
<td>3,113 GWVs; 3,439 nondeployed personnel; female %: GWVs, 61% ; non-GWVs, 58</td>
<td>Past-month alcohol use ≥ 1 response in CAGE and of 5 questions on alcohol consequences in the past 6 months</td>
<td>73% GWVs, 60% non-GWVs</td>
<td>Nonresponse bias not assessed; no significant differences of demographic and confounding factors for GWVs and nondeployed</td>
<td>Low</td>
<td>9.6</td>
<td>8.5</td>
<td>Unadjusted</td>
<td>0.97, 1.35</td>
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<tr>
<td>Steele, 2000 (40)</td>
<td>Cross-sectional telephone interview</td>
<td>1998</td>
<td>Kansas, United States</td>
<td>Stratified random sample of US GWVs residing in Kansas</td>
<td>1,548 GWVs and 482 nondeployed comparison group; female %: GWVs, 14 ; non-GWVs, 13</td>
<td>Self-reported, physician-diagnosed alcohol or drug dependence with new onset from 1990 to 1998</td>
<td>65% overall; 93% of eligible GWVs vs. 88% of non-GWVs; 15% of GWV records showed had not served in the GW but reported had, so excluded</td>
<td>Nonresponse bias assessed for demographics and health outcomes; significant differences between responders and nondeployers</td>
<td>High</td>
<td>3.0</td>
<td>2.0</td>
<td>Adjusted</td>
<td>0.65, 3.31</td>
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<tr>
<td>McCauley, 2002 (38)</td>
<td>Cross-sectional telephone interview</td>
<td>1998–1999</td>
<td>United States</td>
<td>Random sample of 3 groups of Army or NG veterans living in 5 states, and serving or not within 50 km of the Khamisiyah Iraq munitions site, or nondeployed</td>
<td>653 Khamisiyah GWVs; 610 non-Khamisiyah GWVs; 516 nondeployed personnel; female %: Khamisiyah GWVs, 61.1% ; non-Khamisiyah GWVs, 85.1% ; non-GWVs, 10.7</td>
<td>Self-reported, physician-diagnosed alcohol or substance abuse diagnosed since the GW</td>
<td>78% of Khamisiyah GWVs; 75% of non-Khamisiyah veterans; 70% of non-GWVs; 95.1% of deployed males, 89.3% of nondeployed males</td>
<td>Nonresponse bias was assessed for demographics and health outcomes; significant differences between responders and nondeployers</td>
<td>High</td>
<td>4.1 for Khamisiyah and 3.6 for non-Khamisiyah</td>
<td>Adjusted</td>
<td>0.9, 3.4</td>
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<td>Ikin, 2004 (19)</td>
<td>Cross-sectional in-person structured diagnostic interview by psychologist</td>
<td>2000–2002</td>
<td>Australia</td>
<td>Australian GWVs and random sample of nondeployed active duty personnel matched by age, gender, and service (Navy, Army, Air Force)</td>
<td>1,381 GWVs and 1,377 nondeployed personnel; female %: GWVs, 54 ; non-GWVs, 26</td>
<td>CIDI using DSM-IV criteria to assess 12-month prevalence of substance use disorder first present post-GW</td>
<td>81% of GWVs, 57% of non-GWVs; 97% of GWVs and 89% of the comparison group participants completed a psychological interview</td>
<td>Participation bias assessed: significant differences between responders and nonresponders regarding demographics but not health outcomes</td>
<td>Low</td>
<td>19.8</td>
<td>12.6</td>
<td>Adjusted</td>
<td>1.5</td>
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<td>Fiedler, 2006 (20)</td>
<td>Cross-sectional telephone structured diagnostic interviews</td>
<td>2000–2001</td>
<td>United States</td>
<td>Random sample of all US GWVs and nondeployed era personnel</td>
<td>967 GWVs, 784 era veterans, 12</td>
<td>CIDI-SF using DSM-IV criteria to assess 12-month alcohol, drug, any dependence</td>
<td>59% of GWVs, 51% of era nondeployed</td>
<td>Nonresponse bias assessed: significant differences, with increased whites and NCOs responding</td>
<td>Low</td>
<td>4.6</td>
<td>3.1</td>
<td>Unadjusted</td>
<td>0.91, 2.49</td>
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<td>Murphy, 2006 (39)</td>
<td>Cross-sectional postal survey, not framed in GW deployment context, study of screening questionnaires in the military</td>
<td>2001</td>
<td>United Kingdom</td>
<td>Stratified random sample of United Kingdom Armed Forces services (Army, Navy, RAF) by service and size of unit: GWV status determined by record linkage</td>
<td>308 GWVs, 1,339 non-GWs; female %: GWVs, 50.6 ; non-GWVs, 48</td>
<td>AUDIT questionnaire, questions 1 and 2 modified to include a higher category of units consumed</td>
<td>Overall record linkage for 57%</td>
<td>Nonresponse bias not assessed; comparison between GWVs and non-GWVs showed significant differences on service and slightly more males in the GWVs group</td>
<td>Low</td>
<td>7.4</td>
<td>6.6</td>
<td>Adjusted</td>
<td>0.46, 1.94</td>
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<tr>
<td>Study Design</td>
<td>Study Date</td>
<td>Location</td>
<td>Sample Size</td>
<td>Measure/Definition</td>
<td>Participation Assessment</td>
<td>Risk of Bias</td>
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<td>Cross-sectional</td>
<td>1998–2001</td>
<td>United States</td>
<td>1,061 GWVs and 1,128 nondeployed personnel</td>
<td>CIDI using DSM-IV criteria to assess substance dependence of GW-Era onset (1991–1993)</td>
<td>Nonresponse bias assessed; no significant differences on demographics but not on health outcomes</td>
<td>Low 4.3</td>
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<td>Cross-sectional</td>
<td>2004–2005</td>
<td>United States</td>
<td>6,111 GWVs and 3,859 nondeployed personnel</td>
<td>PHQ-9 criteria to assess probable alcohol abuse in the past 6 months</td>
<td>Nonresponse bias assessed; no significant differences on demographics but not on health outcomes</td>
<td>Low 16.4</td>
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<td>Cross-sectional</td>
<td>2007–2008</td>
<td>United States</td>
<td>2,000 GWVs and 2,000 nondeployed personnel</td>
<td>AUDIT, PHQ-9 criteria to assess alcohol and drug use in the past 6 months</td>
<td>Nonresponse bias assessed; no significant differences on demographics but not on health outcomes</td>
<td>Low 4.3</td>
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<tr>
<td>Cross-sectional</td>
<td>2010–2011</td>
<td>United States</td>
<td>2,000 GWVs and 2,000 nondeployed personnel</td>
<td>CIDI using DSM-IV criteria to assess substance dependence of GW-Era onset (1991–1993)</td>
<td>Nonresponse bias assessed; no significant differences on demographics but not on health outcomes</td>
<td>Low 4.3</td>
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**Abbreviations:** AUDIT, World Health Organization Alcohol Use Disorder Identification Test; CAGE, Cut-down, Annoyed, Guilty, Eye-opener; CI, confidence interval; CIDI, World Health Organization Composite International Diagnostic Interview; CIDI-SF, CIDI-Short Form; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; GW, Gulf War; GWV, Gulf War veteran; NCO, noncommissioned officer; NG, National Guard; OR, odds ratio; PHQ, Patient Health Questionnaire; RAF, Royal Air Force; RR, relative risk.
Study selection and data extraction

The search strategy and selection of studies were conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations (23). Records were identified and duplicates were removed. These records were screened to identify studies for full-text review by the specified inclusion and exclusion criteria above. Quantitative and other relevant data for each study were extracted by standard data extraction forms developed for the review and tabulated, including first author, study design, date and location, method of data collection, sample size including female percentage, alcohol or substance use measure and case definition used in the study, participation rates, assessment of risk of bias, overall risk of bias assessment (see below) of each individual study, outcome of interest as a prevalence in the Gulf War, Afghanistan, and Iraq War veterans and comparison group, crude association estimates (odds ratios), and adjusted (for potential confounding factors such as age) association estimates (odds ratios) of the same (Table 1). We used the following predefined strategy for extracting data to be included in the meta-analysis. Where more than 1 paper from the same study population or the same paper reported the same or a similar outcome measure, priority was given to the most valid and reliable alcohol/substance use case definition. The priority order was as follows: 1) structured diagnostic interview or diagnosis made by a clinician; 2) screening tool; and 3) self-reported physician diagnosis (24, 25). If 2 papers reported an overlapping sample of participants, we prioritized inclusion of results of the larger sample in the meta-analyses. Data were extracted by H. L. K. and another member of the research team independently, and any discrepancies were resolved through discussion.

Risk of bias assessment

We assessed the overall risk of bias of the studies included in this systematic review using an instrument developed by Hoy et al. (26). This instrument is reported to have a high overall interrater agreement of 91%, with a k statistic (27) representing chance-corrected agreement of 0.82 (95% confidence interval (CI): 0.76, 0.86). Items 1–4 and items 5–10 of this instrument are based on the external and internal validity of the included study, respectively. We included an additional item on the availability of, and adjustment for, possible confounding factors since it was expected that there would be considerable variation in the extent to which the individual studies attempted to adjust for confounding factors (10). Individual items were assessed as high and low risk of bias and used to assess overall risk of bias. The authors of the tool had deliberately excluded a moderate risk of bias category as testing indicated that this was being used to avoid deciding between high and low risk of bias; subsequently, interrater agreement improved substantially (26).

Analytical strategy

In all meta-analyses (23), we prioritized inclusion of adjusted (for possible confounders such as age, education, branch of service, and duty status) odds ratios over unadjusted odds ratios and unadjusted odds ratios over simple prevalence values. All the measures of association were converted into odds ratios and corresponding 95% confidence intervals for studies that did not present them in the original articles. As heterogeneity of outcome was expected among studies, a random effects meta-analysis (28, 29) for the outcomes alcohol use disorders, substance use disorders, and any substance use disorders was conducted. Statistical heterogeneity was reported by using the I^2 statistic, which indicates variability in results across studies that is due to heterogeneity rather than chance, with higher values representing greater heterogeneity (30). Sources of variability were assessed by subgroup analysis according to the outcome measure used (diagnostic interview; screening tool; self-reported physician diagnosis), adjusted versus unadjusted odds ratios, risk of bias, theater of deployment (Gulf vs. Iraq/Afghanistan), and duty status (regular, reservist) in Iraq/Afghanistan veterans. If results were originally presented separately for personnel deployed to Iraq or Afghanistan, they were tabulated as such. To investigate whether there was a relationship between sources of variability and the magnitude of the odds ratios, we undertook random effects meta-regression (31). Publication bias was assessed by generated funnel plots (32) and using the Egger test for publication bias (30, 33, 34), which was conducted by using Stata, version 12.0, software (StataCorp LP, College Station, Texas) (35). All meta-analyses were performed by using MetaXL, version 1.4 (http://www.epigear.com) (36). Meta-regressions were conducted by using the “metareg” command in Stata (37).

RESULTS

Figure 1 shows that the search yielded 23,533 records, with 14,771 records remaining after removal of duplicates. After abstract review, 253 full-text articles were identified for further review and were reviewed separately in relation to Gulf War or Iraq/Afghanistan psychological disorders’ eligibility. Of these, in relation to Gulf War eligibility, 228 were excluded and, in relation to Iraq/Afghanistan eligibility, 224 were excluded, the reasons for which are identified in Figure 1. Of the 25 primary Gulf War veteran studies identified, a further 16 potentially eligible articles were excluded as they reported only data pertaining to psychological disorders other than alcohol/substance use disorders, leaving 9 studies (6, 7, 19–22, 38–40) to be included in the meta-analyses. Of the 24 primary Iraq/Afghanistan veteran studies identified, 9 studies reported on alcohol/substance use disorders, and 7 discrete studies were included in the meta-analysis. The characteristics of these studies are reported in Tables 1 and 2. Across the Gulf War studies, sample sizes ranged from 308 to 6,111 for Gulf War veterans and from 482 to 3,859 for the nondeployed veterans; sample sizes ranged from 1,443 to 55,114 for Iraq/Afghanistan veterans. The percentage of Gulf War female veterans in these studies was low. It ranged from 0.6% to 22% for Gulf War veterans and from 2.5% to 22% for the nondeployed military comparison groups; the percentage ranged from 3% to 21% for Iraq/Afghanistan veterans and from 4% to 55% for the nondeployed military comparison groups.

The studies included Gulf War veteran cohorts from the United States, United Kingdom, Australia, and Canada in
all 3 services (Navy, Army, and Air Force). The military comparison groups in all the studies were described and defined as nondeployed, that is, not deployed to the Gulf War or Iraq/Afghanistan during the period of operations, rather than other conflict/other deployed personnel, for example, to Germany and Bosnia. The Iraq/Afghanistan War veteran study populations were from the United States, United Kingdom, and Germany. Some of the Iraq/Afghanistan veteran

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of the systematic review, 1990–2014.
Table 2. Study Population, Methods, and Main Results in Evaluation of Alcohol/Substance Use Disorders in Iraq/Afghanistan War Veterans and Nondeployed Military Personnel

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Study Date</th>
<th>Location</th>
<th>Sample Description</th>
<th>No.</th>
<th>Measure/Definition</th>
<th>Participation</th>
<th>Assessment Risk of Bias</th>
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<th>Prevalence in GWVs, %</th>
<th>Prevalence in Comparison Group, %</th>
<th>Association Estimate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bray, 2006 (44)</td>
<td>Cross-sectional, self-report, anonymous survey</td>
<td>2005 United States</td>
<td>Sample comprised eligible active-duty US military personnel; deployment status served in OEF/OIF vs. nondeployed in any operation in last 3 years</td>
<td>16,146 (3,639 Army; 4,627 Navy; 5,117 Marines; 4,524 Air Force)</td>
<td>AUDIT score cutoff at ≥20 indicated alcohol dependence, Heavy alcohol use (≥5 drinks on same occasion once/week or more in past 30 days); any illicit drug use in past year</td>
<td>51.8% overall participants sampled to represent 4 services, all pay grades, and active force worldwide. Data were weighted to represent all active-duty personnel</td>
<td>Low</td>
<td>3.52a</td>
<td>2.29a</td>
<td>Unadjusted OR = 1.54b,c,d</td>
<td>1.1, 2.14</td>
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<tr>
<td>Bray, 2009 (46)</td>
<td>Cross-sectional, self-report, anonymous</td>
<td>2008 United States</td>
<td>Sample comprised eligible active-duty US military personnel; deployment status, combat deployed since September 11, 2001, and served in OEF/OIF vs. not combat deployed since September 11, 2001</td>
<td>28,546 (5,927 Army; 6,637 Navy; 5,117 Marines; 7,049 Air Force; 3,866 Coast Guard)</td>
<td>AUDIT score cutoff at ≥20 indicated alcohol dependence, Heavy alcohol use (≥5 drinks on same occasion once/week or more in past 30 days); any illicit drug use in past year</td>
<td>71.6% overall participants sampled to represent active force and all pay grades worldwide. Data were weighted to represent all active-duty personnel</td>
<td>Low</td>
<td>4.75h</td>
<td>2.73h</td>
<td>Unadjusted OR = 1.78b,c</td>
<td>1.28, 2.45</td>
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<tr>
<td>Hotopf, 2006 (42)</td>
<td>Cohort study, self-report, survey</td>
<td>2004–2006 United Kingdom</td>
<td>Stratified random sample of United Kingdom Armed Forces deployed to Iraq from January to April, 2003 (Operation TELIC 1) and armed forces personnel at the time but not deployed to TELIC 1 (era)</td>
<td>3,936 regular military, 786 reserves deployed to Operation TELIC 1, 4,750 regular military, 800 reserves of era not deployed</td>
<td>AUDIT caseness to assess alcohol consumption and harmful use: cutoff &gt;13 for males and &gt;10 for females</td>
<td>62.3% of deployed, 56.3% of nondeployed</td>
<td>Nonresponse bias assessed (intensive follow-up, late responder/sensitivity analysis, healthy warrior effect) unlikely important differences</td>
<td>Low</td>
<td>25.6</td>
<td>21.1</td>
<td>Adjusted OR = 1.10d</td>
<td>0.99, 1.22</td>
</tr>
<tr>
<td>Jacobson, 2008 (76)</td>
<td>Follow-up survey, US Millennium Cohort Study</td>
<td>2001–2003, and follow-up, 2004–2006</td>
<td>Cohort study participants who completed surveys at both time points and first deployment to Iraq/Afghanistan between baseline and follow-up</td>
<td>26,613 active duty, 21,888 reserves/NG of whom 5,510 deployed with and 5,661 without combat exposure, 37,310 nondeployed, Female %: deployed with/without (4.5/5.5) combat; nondeployed, 55.1</td>
<td>PHQ-2 new-onset alcohol problems at follow-up (≥1 item). CAGE alcohol dependence. Heavy drinking: males &gt;14 and females &gt;7 drinks/week in the past week; Binge drinking: males ≥25 and females ≥4 drinks 1 or more days in the past week or ≥5 drinks on 1 or more days/time in the past year</td>
<td>71.4% for follow-up response rate</td>
<td>Previous evaluations indicate that the cohort is a representative sample, by demographic, mental health, health, and reported exposures</td>
<td>Low</td>
<td>4.8</td>
<td>3.6</td>
<td>Adjusted OR = 1.15d</td>
<td>0.85, 1.26</td>
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Table continues
Table 2. Continued

<table>
<thead>
<tr>
<th>First Author, Year (Reference No.)</th>
<th>Study Design</th>
<th>Study Date</th>
<th>Location</th>
<th>Sample</th>
<th>Measure/Definition</th>
<th>Participation</th>
<th>Assessment Risk of Bias</th>
<th>Overall Risk of Bias</th>
<th>Prevalence in GWVs, %</th>
<th>Prevalence in Comparison Group, %</th>
<th>Association Estimate</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Kline, 2010 (77)</td>
<td>Cross-sectional, anonymous, self-administered predeployment survey</td>
<td>2007–2008</td>
<td>United States</td>
<td>New Jersey NG members undergoing predeployment for Iraq</td>
<td>2,543 NG: 625 had ≥1 prior OEF or OIF deployment since 2001, and 1,910 had no prior OEF/OIF deployment</td>
<td>Alcohol use measures from the DSM-IV-based National Household Survey of Drug Use and Health</td>
<td>95% of eligible study population</td>
<td>Nonresponse bias not assessed. Fewer non-Hispanic whites and more Hispanics than national NG, similar heavy drinking, and drug use. Few race differences in current data</td>
<td>Low</td>
<td>9.0</td>
<td>6.6</td>
<td>Adjusted OR = 1.88&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fear, 2010 (43)</td>
<td>Cohort study survey</td>
<td>2007–2009</td>
<td>United Kingdom</td>
<td>Randomly sampled United Kingdom Armed Forces (Army, Navy, Air Force) deployed to Iraq in 2004–2006 and nondeployed cohort reassessed; samples added those deployed to Afghanistan in 2006–2007 and who joined United Kingdom forces since 2003</td>
<td>8,278 regular military, 1,712 reserves. Deployed 4,203 to Iraq only, 1,123 to Afghanistan only, 1,389 to Iraq and Afghanistan, and 3,555 not deployed to Iraq/Afghanistan. Female %: Iraq, 9.4; Afghanistan, 5.5; Iraq and Afghanistan, 5.7; and nondeployed, 13</td>
<td>10-item AUDIT score cutoff of ≥16 defined hazardous use harmful to health and was termed &quot;alcohol misuse&quot;</td>
<td>Low</td>
<td>15.7</td>
<td>10.9</td>
<td>Adjusted OR = 1.22&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.02, 1.46</td>
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<td>Shen, 2012 (46)</td>
<td>Database analysis on combined personnel and health record sources—US Defense Manpower Data Center and TRICARE</td>
<td>Not stated but after 2006</td>
<td>United States</td>
<td>Unique active-duty US personnel serving between 2001 and 2006 (n = 678,382), with approximately 49% Army, 14% Marines, 20% Navy, and 17% Air Force</td>
<td>Deployed 55,114 to Iraq/Afghanistan, 75,412 to other known OEF/OIF locations, 59,444 to classified/unknown locations, and 488,412 not deployed to OEF/OIF</td>
<td>ICD-9 diagnosis of any substance use/dependence disorder between 2001 and 2006; according to DSM-IV criteria</td>
<td>Not applicable as database analysis. Sample was 25% of Armed Forces</td>
<td>Low</td>
<td>14.8</td>
<td>6.0</td>
<td>Adjusted OR = 4.05&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.82, 4.30</td>
</tr>
<tr>
<td>Vanderploeg, 2012 (62)</td>
<td>Cross-sectional, anonymous, online survey</td>
<td>2009–2010</td>
<td>United States</td>
<td>Current active members of the Florida NG who were deployed to OEF/OIF and not deployed</td>
<td>1,443 deployed to OEF/OIF, 1,655 not deployed</td>
<td>AUDIT to identify excessive drinking behaviors; cutoff referred to article by Hoge (78), which used a 2-item screen</td>
<td>Nonresponse bias not assessed because of survey anonymity. No information on Florida NG cohort available</td>
<td>High</td>
<td>38.4</td>
<td>29.8</td>
<td>Adjusted OR = 0.75&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.57, 1.00</td>
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<tr>
<td>First Author, Year (Reference No.)</td>
<td>Study Design</td>
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<td>Location</td>
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<td>Trautmann, 2014 (41)</td>
<td>Cross-sectional study including clinical assessment and face-to-face diagnostic interviews</td>
<td>2010–2011</td>
<td>Germany</td>
<td>German soldiers examined about 12 months after Afghanistan deployment in 2009–2010; randomly selected never deployed, stratified by age, sex, and unit grid</td>
<td>1,483 deployed to Afghanistan, and 889 never deployed. Female %: deployed and never deployed both, 5.0</td>
<td>Munich-CIDI, DSM-IV criteria to assess alcohol use disorders in the past 12 months: binge drinking (≥7 drinks on an occasion) and heavy drinking (≥24 g of ethanol/day for men, ≥16 g of ethanol/day for women). Self-reported illegal drug use.</td>
<td>92.8% for deployed, 95.4% for never deployed</td>
<td>Eligible and noneligible soldiers were similar. Those never deployed and deployed were comparable</td>
<td>Low</td>
<td>3.6</td>
<td>2.2</td>
<td>1.9(0)</td>
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**Abbreviations:** AUDIT, World Health Organization Alcohol Use Disorder Identification Test; CAGE, Cut-down, Annoyed, Guilty, Eye-opener; CI, confidence interval; CIDI, World Health Organization Composite International Diagnostic Interview; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; GWV, Gulf War veteran; ICD-9, International Classification of Diseases, Ninth Revision; NG, National Guard; OEF, Operation Enduring Freedom; OIF, Operation Iraqi Freedom; OR, odds ratio; PHQ, Patient Health Questionnaire; TELIC 1, the buildup and completion of major combat operations of the 2003 Iraq War from January 18 to June 28, 2003.

Prevalences and unadjusted odds ratios for alcohol dependence, heavy alcohol use, and illicit drug use in the Army, Marines, Navy, and Air Force.

Unadjusted odds ratio calculated in Meta-XL (36), by using reported prevalence and sample sizes, as well as standard errors (obtained from author) for OEF/OIF veterans versus nondeployed group in the last 3 years.

Prevalences and unadjusted odds ratios for possible alcohol dependence in past year, heavy alcohol use, and illicit drug use in the Army, Marines, Navy, and Air Force.

Odds ratios of AUDIT caseness in all subjects, regular military, and reservists, adjusted for age, sex, rank, education, marital status, service, and deployment fitness (reserve status in all subject comparisons) and considered sampling weights.

AUDIT caseness after reassigning era participants to the Iraq War group if they had served in subsequent TELIC 1 deployments versus the nondeployed group adjusted for age, sex, rank, education, marital status, service, and fitness to deploy; and odds ratios of AUDIT caseness of combat versus no combat in regular military in the Iraq War group only, adjusted for the same variables.

Odds ratios of PHQ-defined, new-onset, alcohol-related problems, heavy weekly drinking, and binge drinking in active-duty OEF/OIF deployed veterans with combat exposure versus nondeployed group, adjusted for age, birth year, race/ethnicity, service, history of mental disorders, smoking, and history potential alcohol dependence.

Odds ratios of PHQ-defined, new-onset, alcohol-related problems, heavy weekly drinking, and binge drinking in reserve/NG OEF/OIF deployed veterans with combat exposure versus nondeployed group, adjusted for sex, birth year, race/ethnicity, service, history of mental disorders, smoking, and history potential alcohol dependence.

Odds ratios of alcohol dependence in the past 12 months, binge drinking in the past 6 months, and illicit drug use in the past 12 months in previously deployed OEF/OIF veterans since 2001 versus no prior OEF/OIF deployment, adjusted for age, sex, race/ethnicity, education, income, marital status, and military deployment other than in OEF/OIF.

Odds ratios of alcohol misuse in reserve personnel deployed to Iraq or Afghanistan, Afghanistan only, and both Iraq and Afghanistan versus personnel not deployed to Iraq/Anhafghanistan, and in regular combat versus combat service support and combat support versus combat service support adjusted for age, sex, marital status, education, rank, serving status, and service.

Odds ratios of alcohol misuse in reservist personnel deployed to Iraq or Afghanistan versus personnel not deployed to Iraq/Anhafghanistan, adjusted for age, sex, marital status, education, rank, serving status, and service.

Odds ratios of any substance use/dependence in personnel deployed to Iraq/Anhafghanistan by service branch (Army, Marines, Navy, and Air Force) versus not deployed, adjusted for gender, race/ethnicity, marital status, and age.

Odds ratios of excessive drinking adjusted for the other covariates, that is, demographics, predeployment psychological trauma, physical injury, traumatic experiences, blast exposure, and traumatic brain injury.

Odds ratios of any alcohol use disorder, binge drinking, heavy drinking, and illegal drug use, adjusted for age, sex, marital status, economic situation, education, service length, unit, and rank.
studies considered associations between levels of combat exposure and health outcomes within the deployed group, but the primary comparisons in the meta-analysis are between the deployed and nondeployed groups.

Of the Gulf War studies, 3 used structured diagnostic interviews to determine the caseness of alcohol/substance use disorders (19–21), and 4 used screening tools (6, 7, 22, 39). The other 2 studies (38, 40) used self-reported physician diagnoses. Of the 7 studies for the outcome of alcohol use disorders, 3 studies provided data for an adjusted odds ratio in the published article (19, 21, 39), and the study by Kang et al. (22) provided a relative risk, for which the unadjusted relative risk was converted to an unadjusted odds ratio with 95% confidence interval. Other studies provided usable data in the published article for calculation of an unadjusted odds ratio (6, 7, 20). Of the 3 studies included in the meta-analysis for the outcome of substance use disorders, 2 studies provided data for an adjusted odds ratio (19, 21), and the remaining study provided usable data for calculation of an odds ratio. Another 2 studies (38, 40) provided data on alcohol or drug use disorders combined, which was difficult to separate; thus, they were not included in the meta-analyses of individual outcomes but were included in the analysis of any substance use disorder outcome.

Of the Iraq/Afghanistan veteran studies, 1 used a structured diagnostic interview to determine alcohol/substance use disorder caseness (41), and the remaining 8 studies used screening tools. Hotopf et al. (42) provided informative data on United Kingdom veterans, but the study population formed part of the cohort of a later study of United Kingdom veterans (43) that was included in the meta-analysis. Bray et al. (44, 45) provided on request more precise estimates of standard errors of prevalence to enable us to calculate odds ratios.

Gulf War veteran studies—alcohol use disorders

The overall odds ratio using the random effects model (28, 29) for the 7 included studies was 1.33 (95% CI: 1.22, 1.46), which indicated higher risk of alcohol use disorders in Gulf War veterans compared with nondeployed military personnel. Overall heterogeneity for all studies represented by $I^2$ was 14% (Figure 2). Stratification by caseness indicated that the screening tool subgroup (odds ratio (OR) = 1.30, 95% CI: 1.14, 1.48) and the structured diagnostic interview subgroup (OR = 1.45, 95% CI: 1.17, 1.81) had comparatively similar odds ratios, and meta-regression indicated no statistically significant association with caseness ($P = 0.452$). However, heterogeneity was higher in the subgroup of studies using screening tools ($I^2 = 46\%$ vs. $I^2 = 0\%$). The screening tool subgroup contributed much greater weight in calculating the overall odds ratio than the studies using diagnostic interviews. There were no studies in the self-reported physician diagnosis subgroup for this outcome.

The studies were further stratified on the basis of adjusted versus unadjusted odds ratio estimates, and the odds ratios in both subgroups were comparatively similar (adjusted subgroup OR = 1.38, 95% CI: 1.10, 1.74; unadjusted subgroup OR = 1.31, 95% CI: 1.17, 1.49); the results of meta-regression indicated no statistically significant association with type of odds ratio ($P = 0.815$). Sensitivity analysis indicated that the overall odds ratio did not vary after excluding any individual study for this outcome, and the statistical significance did not change. The funnel plot was visually inspected, and it did not show an obvious lack of symmetry, and the Egger test was not statistically significant ($P = 0.134$).

Gulf War veteran studies—substance use disorders

Three studies (19–21) reported a substance use disorder outcome separately, and the overall odds ratio using the random effects model for these studies was 2.13 (95% CI: 0.96, 4.72; $I^2 = 29\%$). The result was not statistically significant. Sensitivity analysis indicated, after excluding the study by Fiedler et al. (20), that the overall odds ratio decreased to 1.80 (95% CI: 1.09, 2.98) with overall heterogeneity reduced ($I^2 = 0\%$) and that this finding was statistically significant. The study by Fiedler et al. (20) had only 1 subject in the nondeployed group category for the substance use disorders outcome, and this was the reason for excluding it in the

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**Figure 2.** Forest plot illustrating log-transformed odds ratios of alcohol use disorders in Gulf War veterans compared with nondeployed military personnel. CI, confidence interval; OR, odds ratio; $Q$, Cochran’s $Q$. 

*Epidemiol Rev* 2015;37:38–54
sensitivity analysis. All studies used structured diagnostic interviews to define caseness in substance use disorders. Further stratification was not possible because of the small number of studies.

Gulf War veteran studies—any substance use disorder

Many studies included in this review reported dependence or abuse for more than 1 substance (including alcohol) (19–21), and some reported an odds ratio for combined substance use disorders (38, 40), which prompted us to analyze these studies for the outcome of “any substance use disorder.” The overall odds ratio for the 9 studies using the random effects model for any substance use disorder was 1.35 (95% CI: 1.25, 1.46), which was statistically significant and had low heterogeneity of $I^2 = 0\%$, indicating a higher risk of any substance use disorders in Gulf War veterans compared with nondeployed military personnel (Figure 3). Sensitivity analyses indicated that the overall estimate did not change after excluding any individual study. The odds ratio remained statistically significant throughout these analyses. No asymmetry was detected in the funnel plot, and the Egger test was not statistically significant ($P = 0.863$).

Gulf War veteran studies—risk of bias of included studies

All studies were assessed for overall risk of bias. Two (38, 40) of the 9 studies received a high overall risk of bias assessment. None of the 7 studies included in the alcohol use disorder outcome analysis were assessed as having a high overall risk of bias. The summary estimates for any substance use disorders in Gulf War veterans compared with nondeployed military personnel was higher (regular subgroup OR = 1.32, 95% CI: 1.04, 1.68; reservist subgroup OR = 1.58, 95% CI: 1.31, 1.91), although the results of meta-regression indicated no statistically significant association with the duty status of personnel ($P = 0.599$). Stratification by adjusted versus unadjusted odds ratio estimates also did not identify important differences between subgroups (adjusted subgroup OR = 1.29, 95% CI: 1.02, 1.62; unadjusted subgroup OR = 1.66, 95% CI: 1.31, 2.09); results of meta-regression indicated no statistically significant association with type of odds ratio ($P = 0.348$). Stratification by caseness was not possible because all studies except 1 used a screening tool. Sensitivity analysis indicated that the overall odds ratio did not vary after excluding any individual study for this outcome, and the statistical significance did not change. When meta-analysis was restricted to studies at low risk of bias, there was no important change to the odds ratio (OR = 1.45, 95% CI: 1.23, 1.72). The funnel plot was not asymmetrical, and the Egger test was not statistically significant ($P = 0.338$).

Iraq/Afghanistan War veteran studies—alcohol use disorders

For the outcome alcohol use disorders, the overall odds ratio using the random effects model was 1.36 (95% CI: 1.11, 1.66), which indicated higher risk of alcohol use disorders in Iraq/Afghanistan War veterans compared with nondeployed military personnel. Overall heterogeneity for all studies represented by $I^2$ was 77% (Figure 4). The studies were stratified according to the duty status of personnel (regular vs. reservist), and the odds ratio in the reservist subgroup was slightly higher (regular subgroup OR = 1.32, 95% CI: 1.04, 1.68; reservist subgroup OR = 1.58, 95% CI: 1.31, 1.91), although the results of meta-regression indicated no statistically significant association with the duty status of personnel ($P = 0.599$). Stratification by adjusted versus unadjusted odds ratio estimates also did not identify important differences between subgroups (adjusted subgroup OR = 1.29, 95% CI: 1.02, 1.62; unadjusted subgroup OR = 1.66, 95% CI: 1.31, 2.09); results of meta-regression indicated no statistically significant association with type of odds ratio ($P = 0.348$). Stratification by caseness was not possible because all studies except 1 used a screening tool. Sensitivity analysis indicated that the overall odds ratio did not vary after excluding any individual study for this outcome, and the statistical significance did not change. When meta-analysis was restricted to studies at low risk of bias, there was no important change to the odds ratio (OR = 1.45, 95% CI: 1.23, 1.72). The funnel plot was not asymmetrical, and the Egger test was not statistically significant ($P = 0.338$).

Concerning the aspect of substance use disorders:

For the outcome substance use disorders, the overall odds ratio using the random effects model was 1.14 (95% CI: 1.04, 1.25), which indicated higher risk of substance use disorders...
in Iraq/Afghanistan War veterans compared with nondeployed military personnel (Figure 5). There was no statistical heterogeneity ($I^2 = 0\%$), so subgroup analyses were not necessary. Sensitivity analyses indicated that the overall odds ratio did not vary after excluding any individual study for this outcome, and the statistical significance did not change. We could not perform a sensitivity analysis based on study risk of bias as all studies were rated at low risk of bias. The funnel plot was symmetrical, and the Egger test was not statistically significant ($P = 0.476$).

Iraq/Afghanistan War veteran studies—any substance use disorder

The report by Shen et al. (46) was the only study that measured an “any substance use” outcome in Iraq/Afghanistan veterans, and combining these results with the alcohol use or substance use disorder results of other studies produced a meta-analysis with very high heterogeneity ($I^2 = 98\%$), which we were unable to explain with subgroup analyses (duty status of personnel (regular vs. reservist), adjusted vs. unadjusted subgroup, structured diagnostic interview vs. screening tool for identifying caseness, sensitivity analysis, or risk of bias) (results available on request). Therefore, we considered it more appropriate to report the results of Shen et al. (46) separately. Shen et al. (46) found a higher risk of any substance use disorder in Army (OR = 4.05, 95% CI: 3.82, 4.30), Marine (OR = 4.36, 95% CI: 3.82, 4.97), Navy (OR = 1.77, 95% CI: 1.45, 2.16), and Air Force (OR = 1.76, 95% CI: 1.56, 1.99) veterans of the Iraq/Afghanistan wars compared with nondeployed military personnel.
Comparison of Gulf War veteran studies with Iraq/ Afghanistan War veteran studies

Results of meta-regressions suggested that there was no statistically significant association between theater of war and the odds ratio for alcohol use ($P = 0.862$) or substance use ($P = 0.053$).

DISCUSSION

Our systematic review and meta-analysis found that Gulf War veterans and Iraq/Afghanistan veterans were at a greater risk of alcohol use disorders than military personnel who were not deployed to the Gulf War or to the Iraq War/Afghanistan, respectively. The summary estimate of the likelihood of alcohol use disorders was slightly higher, but not statistically significant, in reservists compared with regular personnel deployed to Iraq/Afghanistan. Veterans of the Iraq War/ Afghanistan were at increased risk of substance use disorders, but it was difficult to draw definitive conclusions regarding substance use disorders in Gulf War veterans because 3 studies reporting this outcome were available, and the elevated meta-analytical estimate had very wide confidence intervals. Our meta-analysis also suggests that Gulf War veterans are at a significantly increased risk for any substance use disorder than military personnel who were not deployed to the Gulf War. The results from alcohol and any substance use disorder outcomes were robust to the impact of risk of bias, publication bias, and our sensitivity analyses. Our systematic review and meta-analysis included studies across veteran cohorts from the United States, United Kingdom, Australia, Germany, and Canada, the majority of which sampled across all 3 services. We are not aware of any previous systematic reviews that have estimated comprehensively the risk in Gulf War and Iraq/Afghanistan veterans.

Our review assessed the included studies on the basis of measures to determine the caseness of alcohol use and substance use disorders. The measures used in the studies included the World Health Organization Composite International Diagnostic Interview (CIDI) (47), CIDI-Short Form (48), CIDI-Munich (41), Primary Care Evaluation of Mental Disorders Patient Health Questionnaire (49), Cut-down, Annoyed, Guilty, Eye-opener Questionnaire (50), World Health Organization Alcohol Use Disorder Identification Test (51), questions to assess heavy drinking and binge drinking (44, 45), questions/algorithms based on the Diagnostic and Statistical Manual of Mental Disorders National Household Survey of Drug Use and Health, health-care provider International Classification of Diseases, Ninth Edition, diagnosis of alcohol disorders, and self-reported physician-diagnosed alcohol or drug dependence. The measures that were based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (52), diagnoses such as the CIDI and CIDI-Short Form can be considered more valid and comparable than the other forms of measurement (53–55). Our review found that studies of Gulf War veterans that had used screening tools in assessing alcohol use disorder had an increased heterogeneity compared with studies that used Diagnostic and Statistical Manual of Mental Disorders–based structured diagnostic interviews. The $I^2$ value for the screening tool subgroup was close to a moderate category (50%), according to the criteria stated by Higgins et al. (30). Systematic reviews by Gaderman et al. (56) of depression among US military personnel and of post-traumatic stress disorder associated with combat exposure in deployment to Iraq or Afghanistan by Kok et al. (57) found heterogeneity due to variation of the measures used to ascertain the outcome, particularly if the screening tools differed in their sensitivity and specificity. Our review included only 2 studies with self-reported physician-diagnosed alcohol or drug dependence, a case definition generally considered less valid and reliable, compared with screening tools and structured diagnostic interviews (24, 25, 58), and this may also have reduced heterogeneity among the measures. Self-report of outcomes has been previously observed as a limitation of research in the field of veterans’ health (56, 57). There were not enough studies to perform subgroup analysis by caseness in Iraq/Afghanistan veteran studies, as all studies except that by Trautmann et al. (41) (which used the CIDI diagnostic interview) used a screening tool (e.g., the Alcohol Use Disorder Identification Test).

The studies included in this systematic review and meta-analysis used the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, as the basis of diagnosis, because the time frame in which they were conducted predated the advent of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. For example, “nicotine” in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, has been replaced by “tobacco” in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, an important change because nicotine replacement is frequently used as a treatment for tobacco use disorder, and nicotine is perhaps not the only addictive component of tobacco. In another related development, the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, has combined substance abuse and substance dependence into the single category of substance use disorder. These changes, however, while worthy of note, do not materially affect the current results.

The funnel plots for alcohol disorders and any substance use disorders in Gulf War veterans were found to be symmetrical on visual inspection, with the latter outcome having a much better symmetry than the former. Despite this, and despite our comprehensive search strategy, we may have failed to identify some studies. The judgment that there is no publication bias on visual inspection of funnel plots can be challenged as subjective, particularly when there is a lower number of studies (59, 60). Therefore, we used more the objective Egger test for publication bias. It was nonsignificant, allowing us to conclude that this had little influence on our overall estimates. Nevertheless, most statistical tests for small study associations are known to have low power, so the presence of publication bias cannot be completely excluded (61).

We assessed the robustness of the results to risk of bias that was not performed in other reviews (10, 15, 56, 57) of a similar nature. However, many of these reviews discussed the essential biases of included studies individually. Our estimates did not vary greatly for overall risk of bias assessment based on 2 subgroups, low and high overall risk of bias. In most of the studies, study samples were representative of the target population, except for 3 studies (38, 40, 62). Many sampling
frames were based on military databases that increased the representativeness of both deployed and nondeployed groups; potential selection bias due to characteristics of the veterans selected for deployment, however, has to be considered (10). All studies included in this review, except for the 2 anonymous surveys of US military personnel by Bray et al. (44, 45), had adjusted for possible confounding factors such as age, sex, rank, service type, and duty status in their published analyses, which addresses this concern to an extent. Only the studies by Ikin et al. (19), Goss Gilroy, Inc. (6), the Iowa Persian Gulf Study Group (7), Fear et al. (43), and Trautmann et al. (41), however, were assessed as having either minimal nonresponse bias or statistically assessed the effect of nonresponse bias in the 2 groups. The participation rate in many studies was lower in the nondeployed comparison group compared with the deployed group, which may reflect their decreased engagement/interest. A similar finding was reported by Stimpson et al. (10) who attributed this to general publicity surrounding illness in Gulf War veterans. We can postulate that differing response rates may have introduced a bias comparable to that reported in the review by Stimpson et al. (10). Murphy et al. (39) discussed a related issue in their study that hypothesized that Gulf War veterans were more likely to report symptoms than the nondeployed era veterans, and they suggested that question framing can introduce a reporting bias. In their study, military personnel were not asked directly about their 1991 service history; rather, it was acquired through a record linkage to determine who had served in the Gulf theater. The authors concluded that, even in the absence of framing, there was a difference between Gulf War and non-Gulf War veterans for physical symptomatic measures. However, this difference was not found for psychological measures. These researchers attributed this increased reporting of physical symptoms without increased reporting of psychological symptoms to reluctance of individuals to report psychological symptoms (even if they are present) within a military context, unless the study explicitly specifies that it is investigating deployment to the Gulf War, which is considered more socially acceptable (39). However, our systematic review and meta-analysis has shown that, in veteran populations deployed to conflicts in a similar region of the world but disparate in time and circumstances, the likelihood of alcohol use disorders is increased compared with that in nondeployed military populations.

Our rigorous methodology of including only studies with a military nondeployed comparison group eliminated many methodological concerns of the previous reviews that had included papers which used civilian comparison groups. We also excluded several well-conducted prevalence studies that did not have any military comparison group, since comparing prevalence studies using different methodologies makes it very difficult to ascertain whether the differences in associations were due to difference in deployment or the different methodologies used in the studies rather than comparison with a similar but nondeployed military group (23). We excluded treatment-seeking, self-selected populations that are more likely to experience higher rates of disorders and may not be representative of the overall military population that was deployed. It is important to acknowledge that only 3 studies that had reported substance use disorders in Gulf War veterans separately (and 4 in Iraq/Afghanistan veterans) matched our review criteria. However, our extensive search methodology made it very unlikely that we missed relevant literature.

Regarding the implications of these findings, an important finding from the current review is that alcohol use disorder and substance use disorders are elevated in troops deployed to the Middle East area of conflicts over the past 20 years. The most likely reason is that alcohol and other drugs are being used to “self-medicate”—to ameliorate other psychological or physical problems (63). Given the high rates of depression and other mental health conditions in troops deployed to the Gulf War (10) and to Iraq and Afghanistan (64), this seems a plausible explanation. Although the small numbers of studies of substance use disorders in Gulf War veterans limited power to detect a difference among the study groups, the stigma around illicit substances may also have resulted in some underreporting of other substance abuse, as the military handles legal substances, alcohol and tobacco, very differently from illicit substances.

Our findings have important policy and program implications. About 697,000 US troops were deployed to the 1991 Gulf War, with other coalition forces (from countries such as the United Kingdom, France, Canada, and Australia) amounting to nearly 260,000 at their peak personnel strength (65). Over 2 million US veterans have deployed to the Iraq and Afghanistan conflicts (66) in a coalition of 49 countries with the United Kingdom providing the second largest force. Increased risk of any condition in veteran populations of these sizes is clearly a concern. Although other disorders such as post-traumatic stress disorder and depression have been the primary focus, it is also important that the elevated risk of substance use disorders in veterans is recognized as there is a strong association between those disorders and substance use disorders (67, 68). Furthermore, individuals with post-traumatic stress disorder and depression occurring at the same time with substance use disorders often have worse treatment outcomes (69). Substance (and alcohol) use disorders are particularly troubling because of the powerful impact on behavior, on the individual’s health, and the impacts on family, community, and society as a whole, in addition to the difficulties in diagnosis and management of comorbid disorders (70). Wells et al. (66) highlighted concerns and argued that veteran health policy should be more focused on reducing stigma, eliminating barriers to care, and increasing viable options for assistance to deployed veterans. Wells et al. (66) also suggested that veterans would benefit from improved screening and resilience training (pre- and postdeployment), primary care recognition and early intervention, and specialized treatment programs. Although we recognize that the value of population screening for mental health issues in postdeployment military populations is a matter of debate (71), it is widely used and does have the potential to identify those with emerging problems (64). This improved early recognition and access to care may serve to reduce the development of maladaptive coping strategies such as substance abuse.

The growing body of evidence regarding the impact of comorbidity on the treatment of psychological disorders (67, 70, 72–75) and the additive effect of substance use disorders and depression among suicide decedents (70) highlight the
importance of early identification of substance use problems and an integrated approach to treating these veterans (68). Our findings indicate that Gulf War and Iraq/Afghanistan veterans are at higher risk of alcohol use disorder and that Iraq/Afghanistan veterans are at higher risk of substance use disorder than nondeployed personnel, but further studies with increased power are needed to assess the robustness of estimates for substance use disorder in Gulf War veterans.

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Author affiliations: Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia (Helen Louise Kelsall, Millawage Supun Dilara Wijesinghe, Dean Philip McKenzie, Andrew Benjamin Forbes, Matthew James Page, Malcolm Ross Sim); Environmental and Occupational Health Unit, Ministry of Health, Colombo, Sri Lanka (Millawage Supun Dilara Wijesinghe); and Department of Psychiatry, University of Melbourne, Parkville, Victoria, Australia (Mark Christopher Creamer).

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