

# Depression in Gulf War veterans: a systematic review and meta-analysis

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**Background.** Although post-traumatic stress disorder (PTSD) has been a focus of attention in 1990/1991 Gulf War veterans, the excess risk of depression has not been clearly identified. We investigated this through a systematic review and meta-analysis of studies comparing depression in Gulf War veterans to depression in a comparison group of non-deployed military personnel.

**Method.** Multiple electronic databases and grey literature were searched from 1990 to 2012. Studies were assessed for eligibility and risk of bias according to established criteria.

**Results.** Of 14 098 titles and abstracts assessed, 14 studies met the inclusion criteria. Gulf War veterans had over twice the odds of experiencing depression [odds ratio (OR) 2.28, 95% confidence interval (CI) 1.88–2.76] and dysthymia or chronic dysphoria (OR 2.39, 95% CI 2.0–2.86) compared to non-deployed military personnel. This finding was robust in sensitivity analyses, and to differences in overall risk of bias and psychological measures used.

**Conclusions.** Despite divergent methodologies between studies, depression and dysthymia were twice as common in Gulf War veterans and are important medical conditions for clinicians and policymakers to be aware of in managing Gulf War veterans' health.

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## Introduction

Major depressive disorder (MDD) is the second leading cause of disability worldwide, contributing 8% of all years lived with disability (YLDs) in 2010 (Vos *et al.* 2012). In comparison, anxiety disorders contribute 3.5% of all YLDs. Exposure to stressful events, such as war, is an established risk factor for depression (Gadermann *et al.* 2012) and research has consistently demonstrated that military personnel deployed to war zones experience increased rates of psychological disorders (Magruder & Yeager, 2009). However most research in this field has focused on post-traumatic stress disorder (PTSD); substantially less has focused on depression,

even though depression is more prevalent than PTSD in veteran populations (Ikin *et al.* 2004; Fiedler *et al.* 2006).

The Gulf War deployment was characterized by short air/ground wars, specific exposures (e.g. oil-well fire smoke, dust, chemical warfare agents, use of nuclear/chemical/biological protective suits, entering/inspecting enemy equipment; Kang *et al.* 2000; Glass *et al.* 2006), stressful experiences among naval personnel, including fear/threat of entrapment below waterline, fear of death, or threat of nuclear/chemical/biological agent attack (Ikin *et al.* 2005), multiple vaccinations, prophylactic agents against nuclear/chemical/biological agent attack, pesticides and depleted uranium (Kang *et al.* 2000).

In 2003, a systematic review of common mental disorders (defined as depression or anxiety) and PTSD in veterans of the 1990/1991 Gulf War found deployed personnel twice as likely to report common mental disorders compared to non-deployed personnel, and 3.5 times as likely to report PTSD (Stimpson

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*et al.* 2003). In 10 years since the publication of that review, several studies have been published on depression and other psychological disorders in Gulf War veterans, including studies of Australian (Ikin *et al.* 2004; McKenzie *et al.* 2004) and US (Fiedler *et al.* 2006; Toomey *et al.* 2007) Gulf War veterans. In 2012, a systematic review of major depression in US military personnel from 1990 to 2011 found that currently deployed personnel had 2.2 times the odds of reporting major depression whereas previously deployed personnel had 2.5 times the odds of reporting major depression, compared to non-deployed personnel (Gadernann *et al.* 2012). However, that review only examined US personnel and the results were not presented by theatre of operations, that is the results were presented for deployed personnel in general; these personnel may have been deployed to multiple locations and conflicts, which limited interpretation and the review's application. Studies included in the Gadernann *et al.* (2012) review were limited to those with sample sizes of more than 1000 personnel. None of the included studies had used a structured diagnostic interview for assessment of depression. Although there have been numerous individual publications on the psychological health, including depression, of Gulf War veterans, no systematic review of depression in Gulf War veterans has been published. One of the previous reviews in this field examined a more general term of common mental disorders and another included only US personnel and had some methodological limitations.

Undertaking a systematic review assists in drawing conclusions about consistency of the results of studies in relation to depression in Gulf War veterans compared to personnel who were not deployed to a war zone or who were deployed elsewhere. Conducting a meta-analysis and presenting its output produces a visual and comparable summary effect estimate of depression in Gulf War veterans compared with non-deployed military personnel and quantifies this in an overall summary measure.

The current study is the first to review systematically and quantitatively the literature on depression and dysthymia in Gulf War veterans worldwide compared to non-deployed military personnel. We have addressed previous limitations in the field by concentrating on depression as the psychological condition of interest, by only including studies with appropriate comparison groups, by excluding treatment, clinical and help-seeking samples, and by focusing solely on one theatre of operation. By publishing summary estimates on depression and dysthymia, it is easier and quicker for readers, including non-researcher veterans, clinicians and policymakers, to gain an overview of the relevant literature.

## Method

### *Selection criteria and search strategy*

We performed a systematic review of published and unpublished literature from 1990 to December 2012. We searched multiple electronic databases, including Medline, Medline In Process, PsycINFO, Embase, Published International Literature on Traumatic Stress (PILOTS) and the Cochrane Library from 1990 to December 2012, for studies relating to psychological outcomes of military personnel deployed in the Gulf, Afghanistan and Iraq conflicts. The psychological outcome of focus was depression; broad terms related to other psychological outcomes and psychological disorders in general, in addition to deployments to Iraq and Afghanistan, were included in the search strings to capture studies in which depression was not the main focus. This broad search enabled studies not specifically related to depression or to the Gulf War, but reporting relevant data, to be captured.

### *Inclusion criteria*

Studies were included if the following criteria were met:

- (1) The population consisted of military personnel deployed to the Gulf War (1990–1991), Afghanistan (2001–) or the Iraq War (2003–2011), encompassing Army, Navy, Air Force, Marines, Coast Guard, medics, and Reservists/National Guard.
- (2) The study was published in English.
- (3) The outcome of interest was depression, but studies containing any one of the psychological disorders of depression, anxiety disorders including PTSD, or substance or alcohol use disorders were included to ensure that no studies reporting depression were missed.
- (4) The study included an appropriate military comparison group that differed in its level of deployment exposure to the corresponding conflict. Non-deployed personnel were defined as personnel who did not serve in the primary area of conflict, as in previous systematic reviews (Magruder & Yeager, 2009). Other conflict/other deployed personnel were defined as personnel deployed outside the primary area of conflict or to other conflicts (e.g. German-deployed military personnel).
- (5) The study provided enough information to generate an odds ratio (OR) by deployment.

### *Exclusion criteria*

Studies were excluded based on the following criteria:

- (1) The conflict deployed sample was of non-military personnel.

- (2) The study was published in a language other than English.
- (3) The sample was based on clinical or injured or treatment/help-seeking population/s, including studies based on data from Veterans Affairs (VA) treatment facilities.
- (4) No appropriate military comparison group was included (e.g. civilians were used as a comparison group).

A list of free text and Medical Subject Headings (MeSH) terms corresponding to three concepts in the research question was developed. These concepts were:

- (1) A1: Gulf War, Iraq War and Afghanistan War.
- (2) A2: Military personnel, military veterans, military medicine and veterans' health.
- (3) B: Psychological disorders.

The final search strategy was: (A1 or A2) AND (B). Key words varied by database; however, a modified portion of the search string for Medline serves as an example:

(exp Gulf War OR Persian Gulf War OR Desert Storm OR Desert Shield OR exp Military Personnel/ OR exp Military Veterans/ OR military\* OR service personnel or soldier\* OR active duty OR deployed\*) AND (exp depression/ OR (depress\* OR dysthymi\* or melancholi\*)).

### Study selection and data extraction

The search proceeded according to recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher *et al.* 2009). Titles and abstracts from each database were entered into the reference manager software, EndNote version X4. The search of the five databases yielded 14098 titles and abstracts for review (see Fig. 1). Following the removal of duplicates, titles and abstracts were screened to identify studies for full-text review by the specified inclusion and exclusion criteria. J.B. reviewed all titles and abstracts and H.K. conducted a blind review of approximately 10% of titles and abstracts and 100% of the abstracts selected for full-text review and all eligible articles. Any discrepancies were resolved through collaboration.

Quantitative and other crucial data for each individual study were extracted by standard data extraction forms developed for the review (descriptive data, summary measures of effect size, precision and assessment of risk of bias). We used the following protocol for extracting data to be included in the meta-analysis. Where more than one 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 case definition (Gilbody *et al.* 2007; Mitchell *et al.* 2009); the hierarchy was as follows: (1) structured diagnostic interview (Robins *et al.* 1988); (2) screening tool [e.g. the Beck Depression Inventory (BDI); Beck *et al.* 1988]; (3) self-reported physician diagnosis. We prioritized reported adjusted ORs over unadjusted ORs and unadjusted ORs over prevalences. Where results were given for both non-deployed and other-deployed comparison groups, we prioritized results for the non-deployed comparison group.

### Risk of bias assessment

The PRISMA statement (Moher *et al.* 2009) notes that the reporting of assessment of risk of bias in included studies is important in the conduct of systematic reviews. 'Risk of bias' refers to 'systematic error or deviation from the truth, in results or inferences' (Higgins & Green, 2011, p. 8.2). We conducted an assessment of the risk of bias of included studies by a tool that had been developed by Hoy *et al.* (2012) for the assessment of prevalence studies in the Global Burden of Disease Study 2010 (GBD 2010): inter-rater agreement overall 91% and  $\kappa$  statistic 0.82, 95% confidence interval (CI) 0.76–0.86. This tool enables an overall risk of study bias based on assessment of the risk of bias of 10 individual items (five items each assessing external and internal validity) and we included an additional item on availability of, and adjustment for, possible confounding factors (Stimpson *et al.* 2003). Individual items were assessed as high and low risk of bias. The authors of the tool deliberately excluded a moderate category as testing indicated this was being used to avoid deciding between high and low risk of bias. Subsequently, inter-rater agreement improved substantially (Hoy *et al.* 2012).

### Statistical analysis

The prevalence of depression was assessed across studies and sources of variability were assessed by subgroup analysis. As heterogeneity was expected between studies, a random effects meta-analysis, stratified by subgroups according to the outcome measure (diagnostic interview; screening tool; self-reported physician diagnosis), was conducted. We further report separate meta-analyses stratified by risk of bias (high *versus* low) and adjusted *versus* unadjusted ORs. Heterogeneity was indicated by the  $I^2$  index, which is an estimate of the variability in results across studies that is due to heterogeneity rather than chance.  $I^2$  ranges between 0% and 100%, with larger values representing greater heterogeneity (Higgins *et al.* 2003). Meta-analyses were conducted using MetaXL version 1.1 (Barendregt & Doi, n.d.), a tool for meta-analysis in Microsoft Excel.

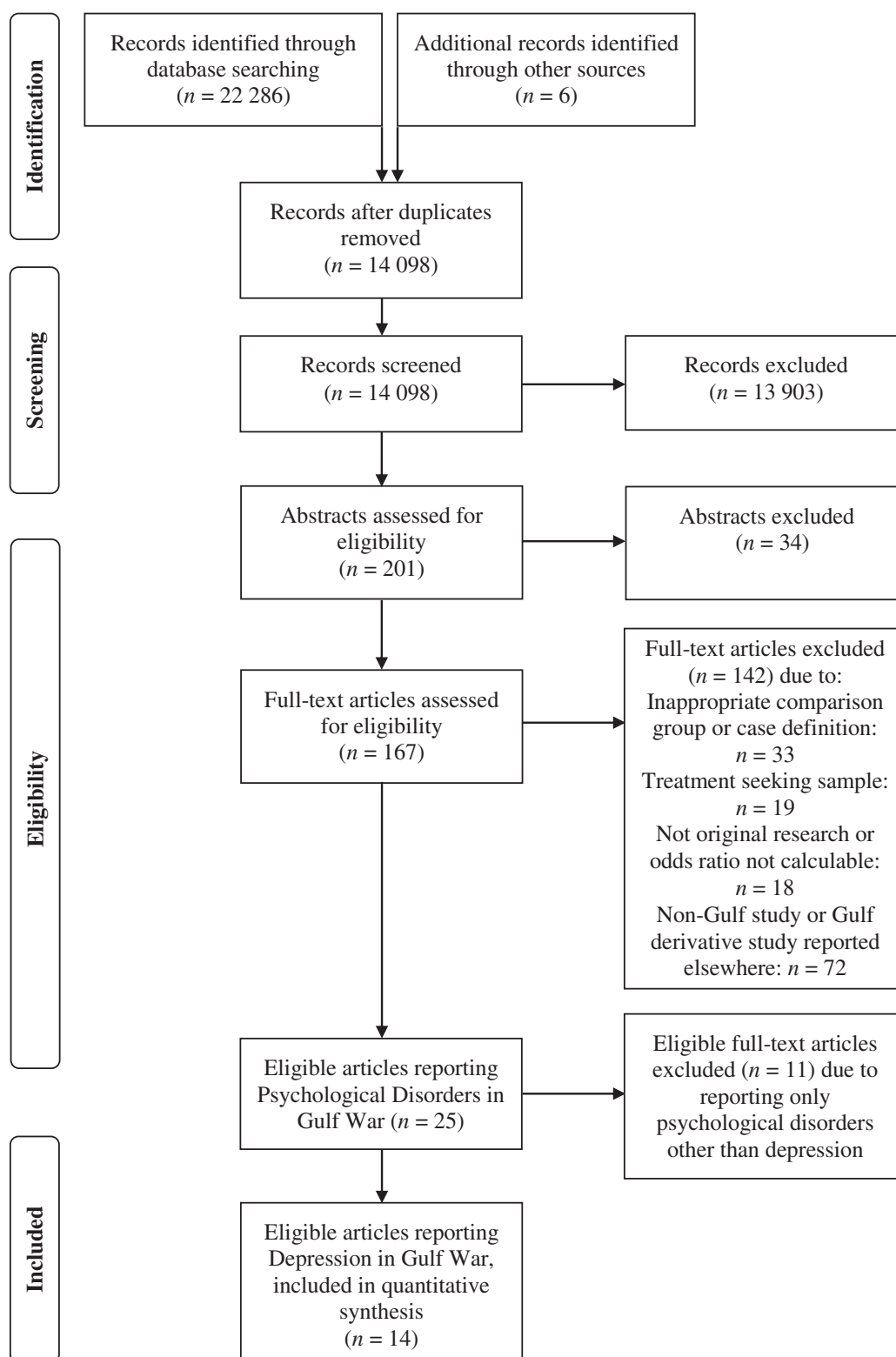


Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart.

## Results

Application of the inclusion and exclusion criteria yielded 201 abstracts for further review (see Fig. 1).

Of these, 34 were excluded based on the abstract, leaving 167 full-text titles for review. Twenty-five articles reported on psychological disorders in Gulf War veterans; of these, 14 (Perconte *et al.* 1993; Sutker *et al.* 1993,

1995; IOWA Persian Gulf Study Group, 1997; Goss Gilroy Inc., 1998; Wolfe *et al.* 1999; Steele, 2000; Gray *et al.* 2002; McCauley *et al.* 2002; Ikin *et al.* 2004; Ishoy *et al.* 2004; Fiedler *et al.* 2006; Toomey *et al.* 2007; Kang *et al.* 2009) reported depression as an outcome and met criteria for inclusion in the quantitative synthesis. Of these 14 studies, four (Wolfe *et al.* 1999; Ikin *et al.* 2004; Fiedler *et al.* 2006; Toomey *et al.* 2007) used structured diagnostic interviews to determine caseness of MDD, dysthymia, or both (three of the four used the CIDI with DSM-IV criteria whereas Wolfe *et al.* used the SCID with DSM-III-R criteria), seven (Perconte *et al.* 1993; Sutker *et al.* 1993, 1995; IOWA Persian Gulf Study Group, 1997; Goss Gilroy Inc., 1998; Ishoy *et al.* 2004; Kang *et al.* 2009) used depression screening tools and three (Steele, 2000; Gray *et al.* 2002; McCauley *et al.* 2002) used self-reported physician diagnosis.

Six of the 14 studies did not present adjusted ORs (Perconte *et al.* 1993; Sutker *et al.* 1993; IOWA Persian Gulf Study Group, 1997; Wolfe *et al.* 1999; Ishoy *et al.* 2004; Kang *et al.* 2009). We attempted contact with the authors to request this information but we were unable to obtain adjusted ORs for any of the six studies. Where studies did not provide an OR, these were calculated using the reported prevalence, or the numbers of deployed and non-deployed veterans with and without depression, using MetaXL 1.1 (Barendregt & Doi, n.d.), and subsequently entered into the meta-analysis along with the adjusted ORs from other studies. Where data were not presented in the desired categories of deployed *versus* non-deployed, the results were recalculated using the reported prevalences and numbers of veterans. Table 1 summarizes these 14 studies in the order of the case definition hierarchy given previously and within each of the groupings the studies were ordered by year of publication. The same order was followed in the forest plots (Figs 2 and 3).

Eight of the 14 studies received a high overall risk of bias assessment (Perconte *et al.* 1993; Sutker *et al.* 1993, 1995; Wolfe *et al.* 1999; Steele, 2000; Gray *et al.* 2002; McCauley *et al.* 2002; Ishoy *et al.* 2004). Common factors contributing to this assessment were poorer depression outcome measures (i.e. self-reported physician diagnosis), poorer sample designs (i.e. convenience samples, non-random sample), lack of adjustment for possible confounding factors, high non-response bias and lack of calculation of ORs. None of the four studies using structured diagnostic interviews were assessed as having a high overall risk of bias.

### Depression and major depression meta-analyses

The forest plot of the studies reporting depression (see Fig. 2) indicates an increased overall odds for

Gulf-deployed compared to non-deployed military personnel reporting depression (OR 2.28, 95% CI 1.88–2.76). Overall heterogeneity, as indicated by  $I^2$ , was high, at 75%. Stratification by case definition reduced the heterogeneity dramatically for the diagnostic interview subgroup ( $I^2=0\%$ ) and the self-report physician diagnosis subgroup ( $I^2=0\%$ ), but less dramatically for the screening tool subgroup ( $I^2=59\%$ ). The OR for the group of studies using a screening tool (2.71, 95% CI 2.23–3.31; Perconte *et al.* 1993; Sutker *et al.* 1993, 1995; IOWA Persian Gulf Study Group, 1997; Goss Gilroy Inc., 1998; Ishoy *et al.* 2004; Kang *et al.* 2009) was higher than the OR for the groups of studies using the diagnostic interview (1.75, 95% CI 1.47–2.01; Wolfe *et al.* 1999; Ikin *et al.* 2004; Fiedler *et al.* 2006; Toomey *et al.* 2007) or the self-report physician diagnosis (1.82, 95% CI 1.49–2.24; Steele, 2000; Gray *et al.* 2002; McCauley *et al.* 2002).

The OR for the diagnostic interview subgroup indicates the odds of Gulf-deployed, compared to non-deployed personnel, reporting major depressive disorder, rather than the more general overall outcome of 'depression', as all of the interview studies used DSM criteria for MDD.

A meta-analysis stratified by adjustment of OR (adjusted *versus* unadjusted) indicated little differences in overall odds of depression between the groups [OR (adjusted subgroup) 2.25, 95% CI 1.4–3.6 *versus* OR (unadjusted subgroup) 2.57, 95% CI 2.2–3.0, forest plot not shown]. Similarly, a meta-analysis stratified by risk of bias (high *versus* low) indicated little differences in the overall odds of depression between the groups [OR (high risk of bias) 2.03, 95% CI 1.71–2.40 *versus* OR (low risk of bias) 2.30, 95% CI 1.75–3.04, forest plot not shown].

### Dysthymia or chronic dysphoria meta-analyses

Five of the 14 studies summarized in Table 1 reported dysthymia (Wolfe *et al.* 1999; Ikin *et al.* 2004; Toomey *et al.* 2007) or chronic dysphoria (IOWA Persian Gulf Study Group, 1997; Goss Gilroy Inc., 1998) as outcomes. The forest plot in Fig. 3 indicates an overall OR of similar magnitude to depression; Gulf War veterans had more than twice the odds of reporting dysthymia or chronic dysphoria compared to non-deployed personnel (OR 2.39, 95% CI 2.0–2.86). The overall heterogeneity between studies was small ( $I^2=0\%$ ). Consistent with MDD, studies using a diagnostic interview to determine caseness (Wolfe *et al.* 1999; Ikin *et al.* 2004; Toomey *et al.* 2007) yielded an overall lower OR (1.83, 95% CI 0.5–6.7) compared to studies using screening tools (IOWA Persian Gulf Study Group, 1997; Goss Gilroy Inc., 1998). The two studies using screening tools contributed much greater weight to

**Table 1.** Gulf War veteran (GWV) health studies investigating depression in GWVs and non-deployed military personnel

First-named author and year	Study design and study period	Sample	Depression case definition and measure	Main results			Comments and risk of bias assessment
				Outcome	GWV prevalence (%)	Comparison group prevalence (%)	
<i>Study samples using diagnostic interview to determine depression caseness</i>							
Wolfe 1999	Cross-sectional in-person structured diagnostic interview administered by trained clinicians; 1994 to 1996	Stratified random sample of two cohorts of US GW-deployed veterans from New England Region (Fort Devens, FD; n=148) and New Orleans (NO; n=56) and a comparison group of air ambulance unit personnel deployed to Germany (G; n=48) during the Gulf War period	SCID non-patient edition using DSM-III-R criteria to assess current (1 month) MDD and dysthymia prevalence	MDD Dysthymia	6.6 (FD) and 4.5 (NO) 3.6 (FD) and 4.8 (NO)	0.0 0.0	Non-response bias assessed in study: yes, for demographics, health outcomes Significant differences between respondents and non-respondents: yes, on demographics and health outcomes Study participation rates: 62% FD (353 eligible); 38% NO (194 eligible); 85% G (eligible numbers not reported) Psychological interview participation rates: 42% FD, 30% NO, 51% G Overall risk of bias: high
Ikin 2004	Cross-sectional in-person structured diagnostic interview administered by trained psychologists; 2000 to 2003	All Australian GWVs (n=1381) and random sample of Navy, Army and Air Force non-deployed active duty personnel (n=1377) matched by age, gender and service type	CIDI using DSM-IV criteria to assess post-Gulf MDD and dysthymia prevalence	MDD Dysthymia	16.7 0.4	11.3 0.3	Non-response bias assessed in study: yes, for demographics, health outcomes Significant differences between respondents and non-respondents: yes, on demographics; no on health outcomes Participation rates: 81% GWVs (1808 eligible); 57% non-GWVs (2796 eligible) Psychological interview completion rates: 78% GWVs; 51% non-deployed Overall risk of bias: low
					MDD unadjusted odds ratio (OR) <sup>a</sup> combining FD and NO GWVs, compared to German deployed comparison group=6.3 (95% CI 0.4–108). Prevalence adjusted for stratification variables (health symptoms and gender)		
					MDD OR 1.6 (95% CI 1.3–2.0) adjusted for service type, rank, age, education, marital status Dysthymia OR 1.4 (95% CI 0.3–7.2) adjusted for service type, rank, age		

Fiedler 2006	Cross-sectional telephone structured diagnostic interview administered by trained interviewers; 2000 to 2001	Random sample ( $n=967$ ) of all US GWVs and non-deployed personnel ( $n=784$ )	CIDI Short Form (SF) using DSM-IV criteria to assess 12-month MDD prevalence	MDD	15.1	7.8	Non-response bias assessed in study: yes, for demographics Significant differences between respondents and non-respondents: yes Participation rates: 59% GWVs (1651 eligible); 51% non-deployed (1552 eligible) Psychological interview completion rate: 55% GWVs; 43% non-deployed Overall risk of bias: low
Toomey 2007	Cross-sectional in-person structured diagnostic interview, administered by trained interviewers; 1998 to 2001	Stratified random subsample of previous study (Kang <i>et al.</i> 2000), US GWVs ( $n=1061$ ) and non-deployed ( $n=1128$ )	CIDI using DSM-IV criteria to assess Gulf-era onset (January 1991 to July 1993) MDD or dysthymia; current depression using BDI-II scores >13 indicating mild (14–19), moderate (17–29) and severe (30–63) depression	MDD Dysthymia	7.1 0.04	4.1 0.0	Non-response bias assessed in study: yes, for demographics, health outcomes Significant differences between respondents and non-respondents: yes, on demographics; no on health outcomes Psychological interview completion rates: 53% GWVs (1996 eligible); 39% non-GWVs (2883 eligible) Overall risk of bias: low
<i>Samples using screening tools to determine depression caseness</i>							
Perconte 1993	Cross-sectional in-person questionnaire administered by VAMC PTSD clinical team; study period not stated	Convenience sample of US reservists from Western Pennsylvania tri-state area GWV ( $n=439$ ), non-deployed comparison group ( $n=126$ ) and Europe-deployed group ( $n=26$ )	BDI-I scores >10 indicating 'minimal depression' (common cut-off scores for BDI-I are 10–18 indicating mild depression, 19–29 indicating moderate depression, 30–63 indicating severe depression)	Depression	26.9	16.7	Non-response bias assessed in study: no Response rates: overall approximately 95% (620 eligible; denominators for GWVs and non-deployed not provided) Overall risk of bias: high
				Unadjusted OR <sup>a</sup>	1.84 (95% CI 1.1–3.1)		

Table 1 (cont.)

First-named author and year	Study design and study period	Sample	Depression case definition and measure	Main results			Comments and risk of bias assessment
				Outcome	GWV prevalence (%)	Comparison group prevalence (%)	
Sutker 1993	Cross-sectional in-person questionnaire administered by VA staff; assessed 4 to 10 months after return	Convenience sample of five US National Guard and Army Reserve Units in US state of Louisiana, with high war-zone stress ( $n=110$ ), low stress (105) and 60 non-deployed personnel	BDI-I scores >10 indicating 'clinical depression'; war zone stress for GWV assessed using Operation Desert Storm (ODS) War-Zone Stress Exposure scale (ODS-SE)	Depression Unadjusted OR <sup>a</sup> 2.4 (95% CI 1.0–5.6)	36.0 (high stress) and 13.0 (low stress)	12.0	Non-response bias assessed in study: no  Response rates: 70% GWVs (306 eligible); non-GWVs not provided Overall risk of bias: high
Sutker 1995	Cross-sectional in-person questionnaire; assessed within 1 year of their return from the Gulf region	912 US military personnel (GWVs=653, non-deployed=259) drawn from overall sample of 1423 Navy, Army, Air Force and Marine National Guard and Reserve Units mobilized for active duty. 511 of 1423 excluded from the analysis. Sample design not-reported	BDI-I scores >10 indicating 'clinical depression'	Depression Unadjusted OR <sup>a</sup> 2.9 (95% CI 1.8–4.5)	22.0	9.0	Non-response bias assessed in study: yes, for demographics Significant differences between respondents and excluded participants: no Response rates: 64% overall (1423 eligible; denominators by serving GWV status not provided) Overall risk of bias: high
IOWA Persian Gulf Study Group 1997	Cross-sectional telephone interview; 1995 to 1996	Stratified random sample of US IOWA state Regular military (R) and National Guard/ Reserve (NG/R) GWVs ( $n=1896$ ) listing IOWA as home state and non-deployed personnel on active duty or activated during the Gulf War ( $n=1799$ ) stratified by age, sex, ethnicity, rank and branch of service	PRIME-MD PHQ based on DSM-III-R criteria assessing 12-month symptoms of MDD and chronic dysphoria	MDD (R) MDD (NG/R) Dysphoria (R) Dysphoria (NG/R) MDD combined unadjusted OR <sup>a</sup> 2.1 (95% CI 1.6–2.7) Dysphoria combined unadjusted OR <sup>a</sup> 1.97 (95% CI 1.45–2.67) Prevalence rate differences adjusted for age, sex, race, branch of military and rank	8.1 10.1 5.3 8.4	3.9 5.3 3.2 4.0	Non-response bias assessed in study: yes, for demographics Significant differences between respondents and non-respondents: yes Response rates: 78% GWVs (2421 eligible); 73% non-deployed (2465 eligible) Overall risk of bias: low



Goss Gilroy Inc. 1998	Cross-sectional postal survey; 1997	All Canadian GWVs (sea, land, air service; $n=3113$ ) and sample of Canadian forces personnel eligible for active duty but non-deployed ( $n=3439$ ), matched on gender, age, regular/reserve status	PRIME-MD PHQ using DSM-III-R criteria to assess current MDD and chronic dysphoria	MDD	18.9 (14.9 <sup>b</sup> )	5.8 (4.9 <sup>b</sup> )	Non-response bias assessed in study: no (however, an assessment was made between GWVs and non-deployed personnel, indicating no significant differences on demographics and confounding factors)
				Chronic dysphoria	10.7 (8.9 <sup>b</sup> )	4.0 (4.3 <sup>b</sup> )	
				MDD adjusted OR 3.67 (95% CI 3.04–4.44), adjusted for rank and income			Response rates: 73% GWVs (4262 eligible); 60% non-deployed personnel (5699 eligible)
				Chronic dysphoria adjusted OR 2.68 (95% CI 2.13–3.35), adjusted for rank, income, branch of service, age and education			Overall risk of bias: low
Ishoy 2004	Cross-sectional in person questionnaire administered by physicians; 1997 to 1998	All Danish Gulf veterans ( $n=686$ ) and random sample of non-deployed comparison group matched on age, gender and profession ( $n=231$ )	SCL-90-R current depression dimension (factor scale, scores of $\geq 3$ on the depression dimension indicating depression)	Depression	11.0	3.9	Non-response bias assessed in study: no (however, an assessment was made between GWVs and non-deployed personnel, indicating no significant differences on demographics but significant differences on health symptoms)
				Unadjusted OR <sup>a</sup> 3.0 (95% CI 1.5–6.2)			Participation rate: 84% (821 eligible) GWVs; 58% non-deployed (400 potential participants)
							Overall risk of bias: high
Kang 2009	Cross-sectional postal and telephone survey; 2004	Follow-up stratified random sample from previous study (Kang <i>et al.</i> 2000) of US GWVs (Navy, Army, Air Force, Marine; $n=6111$ ) and non-deployed personnel frequency matched on gender, branch of service and service status ( $n=3859$ )	PRIME-MD PHQ-9 using DSM-IV criteria to assess current MDD	MDD	14.9	5.8	Non-response bias assessed in study: yes, on demographics, health outcome measures
				Unadjusted OR <sup>a</sup> 2.8 (95% CI 2.4–3.3). Adjusted RR 2.34 (95% CI 2.03–2.70), adjusted for age, gender, race, BMI, cigarette smoking, rank, branch of service, unit component (active duty, national guard/reserve)			Significant differences between responders and non-responders: yes, on demographics; no, on health outcomes
							Response rates: 40% GWVs (15 508 eligible); 27% non-deployed (14 494 eligible)
							Overall risk of bias: low

**Table 1** (cont.)

First-named author and year	Study design and study period	Sample	Depression case definition and measure	Main results			Comments and risk of bias assessment
				Outcome	GWV prevalence (%)	Comparison group prevalence (%)	
<i>Samples using self-reported physician diagnosis to determine depression caseness</i>							
Steele 2000	Cross-sectional telephone interview; 1998	Stratified random sample of US GWVs residing in Kansas ( $n=1545$ ) and non-deployed comparison group ( $n=435$ )	Self-reported physician diagnosis of depression in period from 1990 to 1998	Depression  Adjusted OR 1.85 (95% CI 1.22–2.81), adjusted for age, sex, income and education	12.0	7.0	Non-response bias assessed in study: yes, demographics Significant differences between responders and non-responders: yes Participation rate: 63% overall (3138 eligible) Response rates: 93% GWVs; 88% non-deployed Overall risk of bias: high
Gray 2002	Cross-sectional postal survey; 1997 to 1999	Sample of all US Gulf War-era Seabees (members of US Naval Mobile Construction Battalions; $n=3831$ ) Gulf-era Seabees deployed elsewhere ( $n=4933$ ) and Gulf-era non-deployed Seabees ( $n=3104$ )	Self-reported physician diagnosis of depression diagnosed since 1991; and in past 12 months	Depression  Adjusted OR 1.77 (95% CI 1.41–2.27), adjusted for age, gender, active duty/reserve status, race/ethnicity, current smoking and current alcohol use	7.7	4.6	Non-response bias assessed in study: yes, demographics, health outcomes Significant differences between responders and non-responders: yes, on select demographics; yes on health outcomes Response rates: 63% overall (18 945 eligible); 70% of those located agreed to participate Overall risk of bias: high

McCauley 2002	Cross-sectional telephone interview; 1998 to 1999	Random sample of three groups of US Army or National Guard veterans living in five US states (OR, WA, CA, NC and GA): (1) serving within 50 km of Khamisiyah Iraqi munitions site (KHAM GWV <i>n</i> =653), (2) non-Khamisiyah deployed (GWVs other deployed <i>n</i> =610) and (3) non-deployed personnel ( <i>n</i> =516)	Self-reported physician diagnosed MDD with hospitalization	MDD	1.7	0.6	Non-response bias assessed in study: yes, demographics Significant differences between responders and non-responders: yes Response rates: 71% KHAM GWVs; 38% non-deployed Overall risk of bias: high
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MDD, Major depressive disorder; non-deployed, a military comparison group who were not deployed to the Gulf War during the period of operations; CIDI, World Health Organization Composite International Diagnostic Interview (Robins *et al.* 1988); PRIME-MD PHQ, Primary Care Evaluation of Mental Disorders Patient Health Questionnaire based on DSM-III-R criteria (Spitzer *et al.* 1994); PHQ-9, Patient Health Questionnaire Depression Scale based on DSM-IV criteria (Kroenke & Spitzer, 2002); BDI-I, Beck Depression Inventory-I; BDI-II, Beck Depression Inventory-II; SCL-90-R, Symptoms Check List, Revised Edition (Derogatis & Savitz, 1999); PTSD, post-traumatic stress disorder; VAMC, US Veterans Affairs Medical Center; RR, risk ratio; BMI, body mass index; CI, confidence interval.

<sup>a</sup> Unadjusted OR (random effects model calculated in MetaXL (Barendregt & Doi, n.d.), using reported prevalences and sample sizes for deployed and non-deployed personnel).

<sup>b</sup> Gulf deployed with no other theatre experience.

the calculation of the overall OR than the studies using diagnostic interviews, probably because of the larger sample sizes in the studies using screening tools, although as was also shown in Fig. 2, screening tools generally produced higher ORs than more methodologically rigorous structured diagnostic interviews.

### Discussion

Our systematic review and meta-analyses show that Gulf War veterans were more than twice as likely to experience depression compared with military personnel who were not deployed to the Gulf War. The elevated odds of depression were statistically significant in 13 of the 14 studies that were included. Meta-analyses stratified by risk of bias and by outcome measure demonstrated this finding was robust. The overall odds of Gulf War veterans experiencing dysthymia or chronic dysphoria compared to non-deployed personnel were also doubled, although only five of the 14 included studies investigated these conditions, and three of the five estimates were not statistically significant. In addition, two of the five studies were of chronic dysphoria, rather than the DSM-diagnosed condition of dysthymia.

Our results build on the findings of Gadermann *et al.* (2012) and Stimpson *et al.* (2003), who both found approximately twice the risk of MDD and common mental disorders respectively in deployed, compared to non-deployed, personnel. However Stimpson *et al.* (2003) did not examine anxiety and depression separately and only two studies included in their review used a structured diagnostic interview such as the CIDI or SCID to assess depression. Only one of these two studies met our inclusion criteria (Wolfe *et al.* 1999). We included a further three studies (Ikin *et al.* 2004; Fiedler *et al.* 2006; Toomey *et al.* 2007) published since the Stimpson *et al.* (2003) review that used structured diagnostic interviews. Gadermann *et al.* (2012) only examined US personnel, did not strictly exclude studies without a valid comparison group and did not examine depression separately by theatre of operations. Our review addressed the limitations of previous research in this field and incorporated new studies in finding that there is more than a doubling of risk of depression and dysthymia or chronic dysphoria specifically in Gulf War veterans, rather than deployed groups more broadly.

Our finding was robust to risk of bias, which has not been investigated in previous reviews (Gadermann *et al.* 2012; Stimpson *et al.* 2003). We drew on current epidemiological practice and expert group recommendations (Higgins *et al.* 2011) to use a tool specifically developed for assessing risk of bias in prevalence studies (Hoy *et al.* 2012). We modified the tool in this

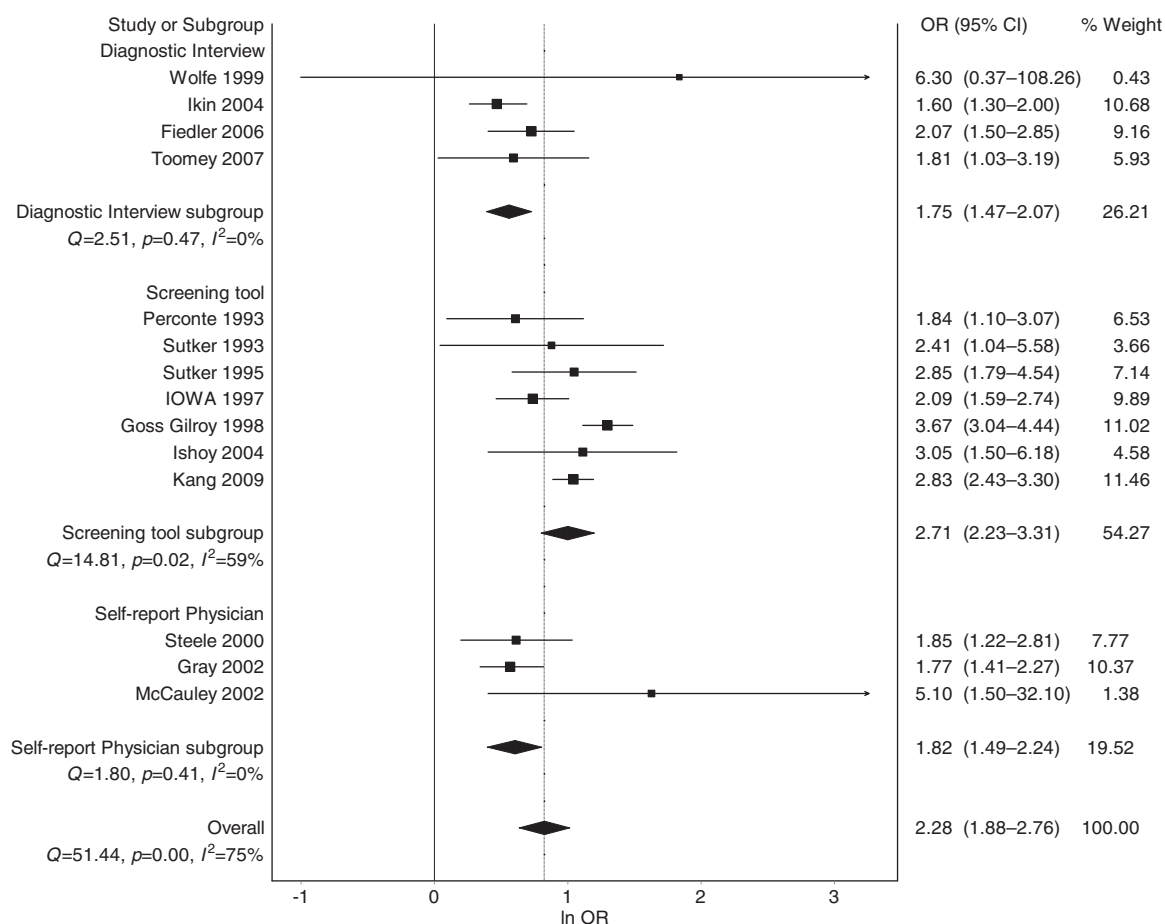


Fig. 2. Random effects meta-analysis forest plot of depression in Gulf War veterans compared to non-deployed military personnel.

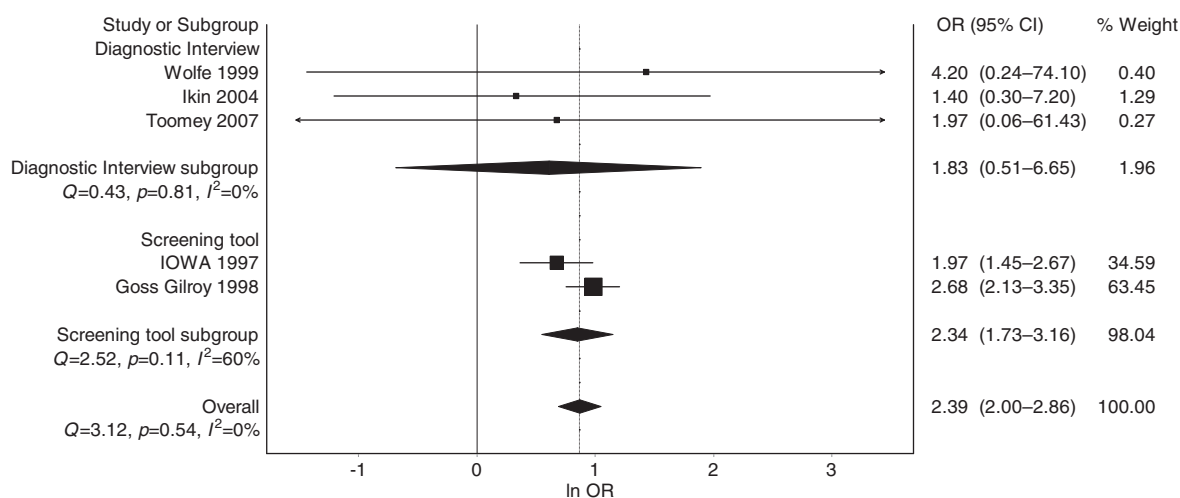


Fig. 3. Random effects meta-analysis forest plot of dysthymia or chronic dysphoria in Gulf War veterans compared to non-deployed military personnel.

study to encompass an assessment of a study's adjustment for possible confounding factors. Our analysis revealed that the overall odds of Gulf War veterans

experiencing depression compared to non-deployed personnel did not change substantially according to the risk of bias. However, a further stratified

meta-analysis indicated that studies using a structured diagnostic interview or self-reported physician diagnosis yielded a lower risk of depression compared to studies using screening tools. This pattern was similar for dysthymia and chronic dysphoria. Importantly, however, the risk of major depression in Gulf War veterans remained significantly elevated when only studies using the most reliable approach (i.e. structured diagnostic interviews) were included in the analysis.

### *Strengths and limitations*

This review is the first systematic review and meta-analysis to focus separately on depression and dysthymia specifically in Gulf War veterans, using a broad search that incorporated recently published studies combined with strict inclusion criteria. Adopting a rigorous approach to the meta-analysis, we were also able to eliminate many of the methodological concerns that have characterized previous systematic reviews. Specifically, only including studies that included a valid comparison group (military non-deployed personnel) meant that the risk of depression in Gulf War veterans was compared to that within a group that was similar other than in their deployment to the Gulf War, rather than using inadequate comparison groups, such as civilians. Similarly, this criterion necessitates that the odds of experiencing depression in deployed compared to non-deployed personnel were generated within studies, rather than between studies. In addition, studies using treatment-seeking populations were excluded, as they are self-selected, probably experience higher rates of depression, and are not representative of the overall military population of that deployment. Although it should be noted that the earlier studies used DSM-III-R criteria and the later ones used DSM-IV, there is no reason to assume this would have influenced the results. The criteria for depressive disorders in these two editions of the DSM were essentially identical.

By using strict inclusion criteria, we potentially exclude well-conducted prevalence studies that did not use a valid military comparison group. Comparing prevalence studies using different methodologies makes it difficult to ascertain whether the differences were due to the exposure/s of interest, or different methodologies. We combined unadjusted and adjusted ORs for confounders in the meta-analysis; however, a further stratified meta-analysis by adjusted *versus* unadjusted ORs indicated that the differences in the ORs were small. The focus of this systematic review was depression. We recognize that many Gulf War veterans and comparison group subjects with depression may also meet criteria for other psychological disorders including PTSD, substance use disorders and anxiety

disorders (Ikin *et al.* 2004). A detailed examination of this co-morbidity, however, was beyond the scope of this review and would detract from the primary focus. The reality is that depression is often ignored in studies of veterans' mental health, which tend to focus on PTSD. By no means all cases of depression will be identified using PTSD-specific measures and an overemphasis on PTSD risks missing substantial psychopathology. It is therefore important to study depression in its own right among veteran populations.

### *Implications of findings*

The findings of this meta-analysis have important implications for our understanding of the relationship between Gulf War service and depression that is important for the medical management of this group of veterans. An earlier systematic review (Stimpson *et al.* 2003) reported an OR of 3.2 for PTSD in Gulf War veterans, a figure comparable to that found for depression in our analysis. It is, perhaps, not surprising that PTSD rates are high because that diagnosis was specifically designed to detect psychiatric disorder following exposure to extreme stress such as military deployment to a combat zone. Our finding that risk of depression is comparably high, however, is of great importance because depression can be missed; if clinicians are looking only for PTSD, they may only find PTSD. In reality, of course, these veterans routinely present with a complex mix of psychiatric and physical problems. The initial challenge is often one of engaging the veteran and developing a therapeutic alliance, before collaboratively generating a treatment plan. To do this, a comprehensive diagnostic formulation is required, and our review should help to highlight the importance of considering depression.

Our review has demonstrated that major depression and dysthymia are important conditions of which clinicians need to be aware when considering treatment plans and management strategies for Gulf War veterans. The impact of depression on engagement in treatment for other conditions, and on social and occupational functioning more broadly, needs to be considered. The findings also have important implications for defense forces and veterans' affairs departments in deployed and veteran health policy and practice, particularly in terms of designing service models. Future research could consider factors that contribute to high overall risk of bias, such as non-random sampling, inadequate case definitions, non-calculation of estimates of effect size or collection of data on and adjustment for confounders.

This study highlights a consistently elevated risk of depression in Gulf War veterans compared to their non-deployed military counterparts. This elevated

risk was robust despite different study methodologies, populations (US, Australian, Danish), branches of service (reservists, navy, air force), psychological outcome measures and sampling designs. The US deployed nearly 700 000 military personnel to the 1990/1991 Gulf War, Australia deployed close to 2000 personnel, the UK deployed approximately 53 000 military personnel, France deployed over 18 000 personnel, Canada deployed over 4000 personnel, Denmark deployed close to 700 personnel and more than 30 other countries provided air, sea or ground forces to the coalition as part of the multinational response to the invasion of Kuwait by Iraq on 2 August 1990. A doubling of the risk of serious and debilitating psychological disorders such as major depression and dysthymia are likely to have a high impact in these veterans and remains a relevant medical problem more than 20 years after the war. Studies in veterans of the Afghanistan and Iraq Wars suggest that these deployed personnel are returning with elevated levels of psychological disorders including depression (Ramchand *et al.* 2008; Wells *et al.* 2011); this study serves as a reminder of the importance of considering depression in assessing veterans' health. A small but growing literature of health in these veterans also suggests a high level of co-morbidity between disorders, such as PTSD, depression, and physical injuries such as traumatic brain injury (Carlson *et al.* 2009). Such findings have important implications for effective treatment for Gulf War veterans.

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### Declaration of Interest

None.

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