Australian Gulf War Veterans' HEALTH STUDY 2003

volume

2

MONASH UNIVERSITY

HSA Health Services Australia

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9. General health

9.1 Aim

The aim of this analysis is to investigate whether male Australian Defence Force personnel who served in the Gulf War have a higher rate of adverse general health outcomes than the comparison group; and, if so, whether these effects are associated with exposures and experiences that occurred in the Gulf War?

9.2 Research questions

1. Do Australian Gulf War veterans have more self-reported health symptoms than the comparison group?
2. Do Australian Gulf War veterans have more self-reported doctor diagnosed or treated medical conditions that were first diagnosed in 1991 or later than the comparison group?
3. Do Australian Gulf War veterans have more self-reported hospitalisations, functional impairment due to illness or injury, and current use of medication than the comparison group?
4. Do Australian Gulf War veterans have poorer general physical and mental health as measured by the SF-12 Health Survey than the comparison group?
5. Do Australian Gulf War veterans have poorer physical health status as measured by body mass index, waist circumference, waist-to-hip ratio, blood pressure, and a fitness test than the comparison group?
6. Where differences in risk of general health outcomes occur between Gulf War veterans and the comparison group, are these associated with exposures and experiences that occurred in the Gulf War?

9.3 Definitions of general health outcomes

These analyses were based on a number of self-reported general health measures such as symptoms and medical conditions, the Short-Form-12 Health Survey (SF-12) and objective physical examination measures such as body mass index (BMI), waist-to-hip ratio (WHR), blood pressure and a fitness test.

In the following description of the definitions used for measuring general health outcomes, the location of the relevant sections and questions of the postal questionnaire (eg G20. Recent health symptoms, q1-63) or medical examination data collection booklet are referred to.

9.3.1 Self-reported symptom definitions

To report the prevalence of self-reported symptoms in the past (G20. Recent health symptoms, q1-63), the response categories for each symptom were combined in two different ways:

- affected subjects were those who reported ‘mild’, ‘moderate’ or ‘severe’ symptoms (‘Mild, moderate or severe = Total Yes’). Non-affected subjects were those who responded ‘not at all’ (‘Not at all = No’);
- affected subjects were those who reported ‘moderate’ or ‘severe’ symptoms (‘Moderate or severe = Yes’). Non-affected subjects were those who responded ‘not at all’ or reported ‘mild’ symptoms (‘Not at all or mild = No’).

9.3.2 Self-reported medical conditions definitions

To report the prevalence of self-reported doctor diagnosed or treated medical conditions (G21. Diagnosed or treated medical conditions, q1-61), information on each reported medical condition was combined with reported year of first diagnosis in two different ways:

- affected subjects were those who reported having first been diagnosed with or treated for the condition in 1991 or later. Non-affected subjects reported never having been diagnosed with or treated for the condition. Subjects who reported being first diagnosed with or treated for the condition prior to 1991 were excluded from this analysis;
- affected subjects were those who reported having been first diagnosed with or treated for the condition in 1991 or later, and the diagnosis they reported was rated by a HSA doctor as 'possible' or 'probable'. Non-affected subjects either reported never having been diagnosed with or treated for the condition, or reported having been first diagnosed with or treated for the condition in 1991 or later but the diagnosis they reported was rated by a HSA doctor as 'non-medical' or 'unlikely'. Subjects who reported having been first diagnosed with or treated for the condition prior to 1991 were excluded from this analysis.

Correct classification of subjects as affected or non-affected depended critically on the accuracy of recall of events that occurred as many as 10 years previously. Restricting the self-reported medical conditions to those assessed by a HSA doctor as being a 'possible' or 'probable' diagnosis, rather than 'non-medical' or 'unlikely', was an attempt to improve the accuracy of classification (see chapter 5 for more detail on the ratings).

9.3.3 Hospitalisations, functional impairment and current use of medication

Hospitalisations were defined as:

- a positive response to question G23. "During the past twelve months have you been hospitalised overnight or longer because of illness or injury?".

Functional impairment was defined as:

- a positive response to question G24. "Thinking back over the past two weeks, did you stay in bed or at home all or part of any day because you did not feel well or as a result of illnesses or injury?"

Current use of any medication was defined as:

- a positive response to question G25. "Are you currently taking any medicines including tablets, creams, inhalers, or other drugs?"

9.3.4 SF-12 Health Survey scoring

The SF-12 Health Survey physical (PCS-12) and mental (MCS-12) component summary scales were scored using US norm-based methods, with separate weights for the physical and mental scales.[258] Both summary scales use the same items but different weights. These weights were constructed by the developers of the SF-12 to produce PCS-12 and MCS-12 scores that would have a mean of 50 and a standard deviation of 10, if applied to the US general population.[258] If desired, scores can be interpreted in terms of the US general population mean of 50. US population norms were used in this report to allow results to be compared with other studies. The items in the scale refer to the four weeks prior to the completion of the questionnaire. The higher the score, the better the physical or mental health status.

9.3.5 Physical health status definitions

9.3.5.1 Body mass index

Body mass index (BMI) was defined as the weight in kilograms divided by the square of the height in metres (kg/m^2) and classified according to the categories used by the National Nutrition Survey.[289]

Table 9.1 Classification of adults according to BMI

Categories	BMI kg/m^2	Risk of related health problems
Underweight	<18.5	Low (but risk of other clinical problems increased)
Normal range	18.5-<20.0	Average
	20-<25.0	
Overweight:	≥ 25.0	
Pre-obese	25.0-<30.0	Increased
Obese class 1	30.0-<35.0	Moderate
Obese class 2	35.0-<40.0	Severe
Obese class 3	≥ 40.0	Very severe

9.3.5.2 Waist circumference and waist-to-hip ratio

Waist circumference, an indicator of increased risk of obesity related complications,[288, 292] was categorised as:

- 'increased risk' - >94 cm
- 'substantially increased risk' - >102 cm

Waist-to-hip ratio (WHR) was calculated by dividing each participant's waist measurement by his hip measurement. A WHR of >0.9 was used to define those at health risk from having a central body fat distribution.[287]

9.3.5.3 Blood pressure

The average of the participant's two systolic and diastolic blood pressure readings were categorised as representative of normal, high-normal or hypertensive blood pressure[294, 295] according to the categories shown in Table 9.2.

Table 9.2 Blood pressure categories according to average systolic and diastolic readings

Category	Systolic (mmHg)		Diastolic (mmHg)
Normal	<130	and	<85
Optimal	<120	and	<80
High-normal	130-139	or	85-89
Hypertension	≥ 140	or	≥ 90
Grade 1 hypertension (mild)	140-159	or	90-99
Grade 2 hypertension (moderate)	160-179	or	100-109
Grade 3 hypertension (severe)	≥ 180	or	≥ 110
Isolated systolic hypertension	≥ 140	and	<90

Where a participant's average systolic and diastolic blood pressure fell into two different categories, the higher category was applied. For example, if a participant's average diastolic

blood pressure was 88 mmHg and average systolic blood pressure was 145 mmHg, he would be categorised as Grade 1 hypertension.

9.3.6 Gulf War exposure measures

Where differences in risk of general health outcomes exist between Gulf War veterans and the comparison group, the analysis will investigate associations with several measures of exposure. The analysis will investigate whether risk of symptoms and medical conditions in either study group differs across subcategories of age, service type and rank. The analysis will also investigate whether risk of general health outcomes within the Gulf War veterans group differs according to the following exposures:

- Deployment completed before or after 17 January 1991 when the air strikes commenced
- Number of immunisations and clustering of immunisations
- Pyridostigmine bromide
- Antimalarials
- Anti-biological warfare tablets
- Pesticides/insecticides
- Repellents
- Being in an area where chemical weapons had been used
- Depleted Uranium
- Military Service Experience questionnaire score.

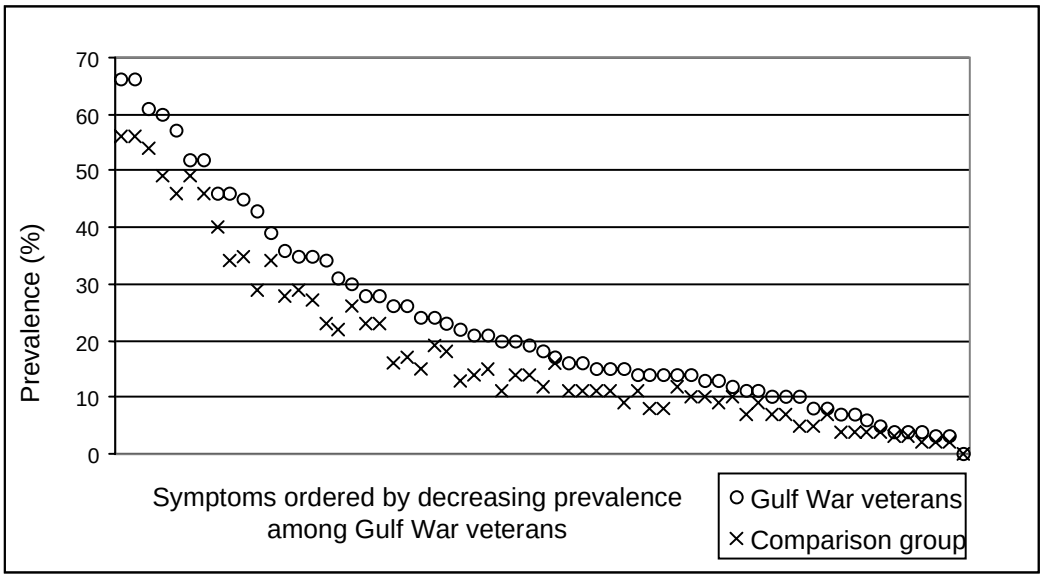
9.4 Results

9.4.1 Symptoms

Table 9.3 presents the prevalence of self-reported symptoms in the past month according to the two definitions of 'mild, moderate or severe = Total Yes' and 'moderate or severe = Yes', and ordered by decreasing prevalence in the Gulf War veteran group. The most common symptoms reported by Gulf War veterans were neuropsychological and musculoskeletal in nature. Gulf War veterans reported all symptoms more frequently than the comparison group, and this difference was statistically significant for all symptoms except those of low back pain, persistent cough, toothache, tender or painful swelling of lymph glands in neck, armpit or groin, vomiting, unintended weight loss greater than 4kg, and seizures or convulsions. The OR is a ratio that compares the odds that the symptom was reported by Gulf War veterans with the odds that members of the comparison group reported the symptom. When calculated with adjustment for these factors, the odds ratio (crude OR) is referred to in the tables as the adjusted odds ratio (Adj OR). Adjustment for potential confounders (age, service type, rank, marital status and education) made minor differences to the value of the odds ratio (OR).

Although there were some slight variations in the order, symptoms that were commonly reported by the Gulf War veteran group were also commonly reported by the comparison group (Figure 9.1).

Figure 9.1 Self-reported symptoms in last month by Gulf War deployment status



When only moderate or severe symptoms were considered (Table 9.3), the proportions of both groups reporting symptoms decreased to approximately one-quarter to one-half of those reporting 'not at all or mild' symptoms, and even more for some symptoms; indicating that the self-reported symptoms were dominated by relatively mild symptoms. For all symptoms except the rare conditions of skin ulcers and seizures or convulsions, the proportion of Gulf War veterans reporting symptoms remained higher than that of the comparison group. For most individual symptoms, the adjusted odds ratios for moderate and severe symptoms were higher than the adjusted odds ratios for any reported symptoms, indicating that when Gulf War veterans reported symptoms, they were more severe in nature. When moderate or severe symptoms only were considered, the adjusted odds ratios decreased for a number of symptoms (ringing in the ears, chest pain, shaking, loss of balance or coordination, loss of control over bladder or bowels, and burning sensation in the sex organs) and these were no longer significant.

Table 9.3 Prevalence and odds ratios (ORs) of self-reported symptoms in the past month ordered by decreasing prevalence in the Gulf War group

	'Mild, moderate or severe = Total Yes'						'Moderate or severe = Yes'			
	GWV	Comp grp					GWV	Comp grp		
Symptom	**n (%)**	**n (%)**	**Crude OR**	**Adj OR***	**95% CI**	**P value**	**n (%)**	**n (%)**	**Adj OR***	**95% CI**
Feeling unrefreshed after sleep	937 (66)	862 (56)	1.5	1.6	1.3-1.8	<0.001	398 (28)	285 (18)	1.7	1.4-2.1
Fatigue	937 (66)	861 (56)	1.5	1.6	1.3-1.8	<0.001	325 (23)	243 (16)	1.6	1.3-1.9
Headaches	872 (61)	828 (54)	1.4	1.3	1.1-1.6	<0.001	291 (20)	205 (13)	1.6	1.3-2.0
Sleeping difficulties	851 (60)	753 (49)	1.6	1.6	1.4-1.9	<0.001	371 (26)	253 (16)	1.8	1.5-2.2
Irritability / outbursts of anger	808 (57)	702 (46)	1.6	1.6	1.4-1.8	<0.001	309 (22)	182 (12)	2.0	1.7-2.5
Low back pain	743 (52)	757 (49)	1.1	1.2	1.0-1.3	0.057	308 (22)	298 (19)	1.2	1.0-1.4
General muscle aches or pains	736 (52)	707 (46)	1.3	1.3	1.1-1.5	0.001	207 (15)	139 (9)	1.7	1.4-2.2
Flatulence or burping	654 (46)	624 (40)	1.3	1.3	1.1-1.5	0.001	209 (15)	141 (9)	1.6	1.3-2.1
Forgetfulness	654 (46)	520 (34)	1.7	1.7	1.5-2.0	<0.001	195 (14)	109 (7)	2.1	1.6-2.7
Difficulty finding the right word	643 (45)	543 (35)	1.5	1.6	1.4-1.8	<0.001	160 (11)	82 (5)	2.3	1.7-3.0
Loss of concentration	611 (43)	448 (29)	1.9	1.9	1.6-2.3	<0.001	144 (10)	78 (5)	2.2	1.6-2.9
Stiffness in several joints	556 (39)	518 (34)	1.3	1.3	1.1-1.5	0.001	215 (15)	175 (11)	1.4	1.2-1.8
Rash or skin irritation	510 (36)	429 (28)	1.5	1.5	1.2-1.7	<0.001	215 (15)	129 (8)	2.0	1.6-2.5
Pain, without swelling or redness, in several joints	498 (35)	453 (29)	1.3	1.3	1.1-1.5	0.001	231 (16)	197 (13)	1.3	1.1-1.6
Itchy or painful eyes	490 (35)	424 (27)	1.4	1.4	1.2-1.7	<0.001	115 (8)	88 (6)	1.4	1.1-1.9
Avoiding doing things or situations	481 (34)	362 (23)	1.7	1.7	1.5-2.1	<0.001	145 (10)	92 (6)	1.9	1.4-2.5
Shortness of breath	445 (31)	339 (22)	1.6	1.6	1.4-1.9	<0.001	103 (7)	52 (3)	2.4	1.7-3.4
Ringing in the ears	430 (30)	398 (26)	1.3	1.3	1.1-1.5	0.002	156 (11)	152 (10)	1.2	0.9-1.5
Indigestion	405 (28)	359 (23)	1.3	1.4	1.2-1.6	<0.001	128 (9)	83 (5)	1.7	1.3-2.3

	'Mild, moderate or severe = Total Yes'						'Moderate or severe = Yes'			
	GWV	Comp grp					GWV	Comp grp		
Symptom	**n (%)**	**n (%)**	**Crude OR**	**Adj OR***	**95% CI**	**P value**	**n (%)**	**n (%)**	**Adj OR***	**95% CI**
Sore throat	392 (28)	353 (23)	1.3	1.3	1.1-1.6	0.001	67 (5)	47 (3)	1.6	1.1-2.4
Feeling distant or cut off from others	372 (26)	244 (16)	1.9	2.0	1.6-2.4	<0.001	121 (9)	77 (5)	1.9	1.4-2.5
Diarrhoea	368 (26)	258 (17)	1.7	1.7	1.4-2.1	<0.001	94 (7)	42 (3)	2.4	1.6-3.5
Feeling jumpy / easily startled	346 (24)	229 (15)	1.9	1.9	1.5-2.2	<0.001	128 (9)	72 (5)	2.1	1.6-2.9
Loss of interest in sex	342 (24)	288 (19)	1.4	1.4	1.2-1.7	<0.001	145 (10)	96 (6)	1.8	1.3-2.4
Chest pain	328 (23)	277 (18)	1.4	1.4	1.1-1.6	0.001	51 (4)	49 (3)	1.1	0.8-1.7
Distressing dreams	306 (22)	206 (13)	1.8	1.8	1.5-2.2	<0.001	116 (8)	56 (4)	2.5	1.8-3.6
Rapid or pounding heart beat	304 (21)	218 (14)	1.7	1.6	1.4-2.0	<0.001	77 (5)	42 (3)	2.1	1.4-3.1
Tingling or burning sensation in hands or feet	294 (21)	237 (15)	1.4	1.5	1.2-1.8	<0.001	88 (6)	60 (4)	1.7	1.2-2.4
Night sweats which soak the bed sheets	290 (20)	176 (11)	2.0	2.0	1.6-2.5	<0.001	113 (8)	59 (4)	2.2	1.6-3.1
Increased sensitivity to noise	277 (20)	213 (14)	1.5	1.6	1.3-2.0	<0.001	98 (7)	72 (5)	1.6	1.2-2.2
Dry mouth	266 (19)	221 (14)	1.4	1.4	1.1-1.7	0.001	64 (5)	38 (2)	1.9	1.2-2.8
Stomach cramps	261 (18)	187 (12)	1.6	1.6	1.3-1.9	<0.001	83 (6)	40 (3)	2.2	1.5-3.3
Persistent cough	240 (17)	243 (16)	1.1	1.1	0.9-1.3	0.358	77 (5)	66 (4)	1.3	0.9-1.8
Wheezing	230 (16)	168 (11)	1.6	1.5	1.2-1.9	<0.001	62 (4)	33 (2)	2.0	1.3-3.1
Increased sensitivity to light	224 (16)	172 (11)	1.5	1.5	1.2-1.9	<0.001	76 (5)	43 (3)	1.8	1.2-2.7
Unintended weight gain greater than 4kg	216 (15)	170 (11)	1.5	1.5	1.2-1.8	0.001	101 (7)	61 (4)	2.0	1.4-2.7
Mouth ulcers	212 (15)	167 (11)	1.5	1.5	1.2-1.9	<0.001	33 (2)	17 (1)	2.2	1.2-3.9
Intolerance to alcohol	209 (15)	134 (9)	1.8	1.8	1.4-2.3	<0.001	85 (6)	48 (3)	2.0	1.4-2.9
Loss of, or decrease in, appetite	204 (14)	167 (11)	1.4	1.4	1.1-1.7	0.006	58 (4)	32 (2)	2.1	1.4-3.4

	'Mild, moderate or severe = Total Yes'						'Moderate or severe = Yes'			
	GWV	Comp grp					GWV	Comp grp		
Symptom	**n (%)**	**n (%)**	**Crude OR**	**Adj OR***	**95% CI**	**P value**	**n (%)**	**n (%)**	**Adj OR***	**95% CI**
Shaking	203 (14)	122 (8)	1.9	1.9	1.5-2.4	<0.001	45 (3)	29 (2)	1.6	1.0-2.6
Dizziness, fainting or blackouts	201 (14)	131 (8)	1.8	1.7	1.4-2.2	<0.001	41 (3)	16 (1)	2.8	1.5-5.0
Toothache	200 (14)	179 (12)	1.3	1.2	1.0-1.5	0.070	52 (4)	32 (2)	1.7	1.1-2.7
Problems with sexual functioning	196 (14)	149 (10)	1.5	1.7	1.3-2.1	<0.001	76 (5)	45 (3)	2.3	1.5-3.4
Skin infections eg. boils	186 (13)	155 (10)	1.4	1.3	1.1-1.7	0.012	54 (4)	34 (2)	1.7	1.1-2.7
Loss of sensation in hands or feet	185 (13)	138 (9)	1.5	1.6	1.3-2.1	<0.001	66 (5)	41 (3)	2.0	1.3-2.9
Passing urine more often	172 (12)	151 (10)	1.3	1.3	1.0-1.7	0.020	60 (4)	37 (2)	1.8	1.2-2.8
Loss of balance or coordination	161 (11)	114 (7)	1.6	1.6	1.3-2.1	<0.001	29 (2)	27 (2)	1.2	0.7-2.1
Constipation	155 (11)	139 (9)	1.2	1.3	1.0-1.7	0.027	38 (3)	23 (1)	1.8	1.0-3.0
Feeling feverish	143 (10)	106 (7)	1.5	1.5	1.2-2.0	0.002	32 (2)	21 (1)	1.8	1.0-3.2
Nausea	139 (10)	114 (7)	1.4	1.4	1.1-1.8	0.016	37 (3)	17 (1)	2.5	1.4-4.5
Feeling disorientated	137 (10)	76 (5)	2.1	2.1	1.6-2.8	<0.001	24 (2)	7 (<1)	4.4	1.8-10.4
Double vision	119 (8)	72 (5)	1.9	2.0	1.5-2.7	<0.001	29 (2)	6 (1)	2.2	1.2-4.1
Tender or painful swelling of lymph glands in neck, armpit or groin	115 (8)	104 (7)	1.2	1.2	0.9-1.5	0.301	35 (2)	15 (1)	2.3	1.2-4.2
Increased sensitivity to smells or odours	102 (7)	57 (4)	2.0	2.1	1.5-2.9	<0.001	32 (2)	17 (1)	2.1	1.2-3.9
Difficulty speaking	95 (7)	68 (4)	1.6	1.5	1.1-2.1	0.013	18 (1)	9 (1)	2.3	1.0-5.2
Lump in throat	89 (6)	68 (4)	1.5	1.5	1.0-2.0	0.026	31 (2)	9 (1)	3.8	1.8-8.1
Vomiting	73 (5)	64 (4)	1.3	1.2	0.8-1.7	0.369	20 (1)	11 (1)	1.9	0.9-4.2

	'Mild, moderate or severe = Total Yes'						'Moderate or severe = Yes'			
	GWV	Comp grp					GWV	Comp grp		
Symptom	**n (%)**	**n (%)**	**Crude OR**	**Adj OR***	**95% CI**	**P value**	**n (%)**	**n (%)**	**Adj OR***	**95% CI**
Loss of control over bladder or bowels	62 (4)	40 (3)	1.7	1.8	1.2-2.8	0.004	12 (1)	7 (<1)	2.2	0.8-5.8
Unintended weight loss greater than 4kg	55 (4)	47 (3)	1.3	1.2	0.8-1.9	0.304	23 (2)	14 (1)	1.8	0.9-3.6
Pain on passing urine	50 (4)	34 (2)	1.6	1.6	1.0-2.5	0.041	8 (1)	3 (<1)	3.5†	0.9-13.6
Burning sensation in the sex organs	49 (3)	24 (2)	2.3	2.2	1.3-3.7	0.002	8 (1)	6 (<1)	1.5	0.5-4.6
Skin ulcers	41 (3)	27 (2)	1.7	1.7	1.0-2.9	0.032	6 (<1)	8 (1)	0.8	0.3-2.2
Seizures or convulsions	5 (<1)	4 (<1)	1.4	1.5†	0.4-5.8	0.544	1 (<1)	3 (<1)	0.5†	0.05-4.9

* Odds ratios are adjusted for service type, rank and age (< 20, 20-24, 25 to 34, ≥35 years), education and marital status.

† Odds ratios are adjusted for service type, rank and age (<25 vs ≥25 years). Confidence intervals and P values for adjusted odds ratios were obtained using exact methods for stratified 2x2 tables.

9.4.1.1 Comparison by service type

Table 9.4, Table 9.5 and Table 9.6 present the prevalence and odds ratios for symptoms most commonly reported by the Navy, Army and Air Force respectively, and ordered by decreasing prevalence in the Gulf War veteran group for each service type. The proportion of Navy Gulf War veterans reporting symptoms and the order of frequency they were reported in was very similar to that of the total Gulf War veteran group. This was to be expected, given the high representation of the Navy in the Gulf War group and its dominance of the pattern of symptom reporting.

The 15 symptoms most commonly reported across the service subgroups were similar. The six most common symptoms tended to be neuropsychological symptoms, and the odds ratios between the study groups for these symptoms were similar across the different service types. The symptoms were also common in the service subgroups of the comparison group. The relatively increased reporting of symptoms by Gulf War veterans was more marked in the younger (<20 year) age group (data not shown). The Army subjects in both study groups reported the common symptoms more frequently than the Navy and Air Force subjects. The order of frequency varied between the service types, and this was most marked in the Air Force compared with the Army and Navy. Within each service type, the proportion of Gulf War veterans reporting symptoms was greater than the comparison group for nearly all symptoms. These differences were statistically significant for all symptoms except low back pain in the Navy subgroup, were not significant for any symptoms in the Army subgroup, and were only significant for loss of concentration in the Air Force subgroup. When adjusted odds ratios for each symptom were compared across service types, no statistically significant differences emerged.

Table 9.4 Prevalence and ORs of the fifteen symptoms most commonly reported by Navy participants in the past month

Symptom	GWV 'Total Yes' n (%)	Comp grp 'Total Yes' n (%)	Crude OR	Adj OR*	95% CI	P value
Feeling unrefreshed after sleep	814 (66)	617 (55)	1.6	1.6	1.4-2.0	<0.001
Fatigue	811 (66)	609 (54)	1.6	1.6	1.4-1.9	<0.001
Headaches	764 (62)	612 (55)	1.4	1.4	1.2-1.6	<0.001
Sleeping difficulties	732 (60)	528 (47)	1.7	1.7	1.4-2.0	<0.001
Irritability / outbursts of anger	707 (58)	510 (46)	1.6	1.6	1.4-1.9	<0.001
General muscle aches or pains	645 (53)	514 (46)	1.3	1.3	1.1-1.6	0.001
Low back pain	642 (52)	550 (49)	1.1	1.2	1.0-1.4	0.073
Flatulence or burping	575 (47)	444 (40)	1.3	1.4	1.2-1.6	<0.001
Forgetfulness	567 (46)	385 (46)	1.6	1.7	1.4-2.0	<0.001
Difficulty finding the right word	565 (46)	387 (34)	1.6	1.7	1.4-2.0	<0.001
Loss of concentration	531 (43)	312 (28)	2.0	2.0	1.7-2.4	<0.001
Stiffness in several joints	480 (39)	383 (34)	1.2	1.3	1.1-1.5	0.003
Rash or skin irritation	445 (36)	320 (29)	1.4	1.5	1.2-1.8	<0.001
Pain, without swelling or redness, in several joints	436 (35)	340 (30)	1.3	1.3	1.1-1.6	0.002
Itchy or painful eyes	426 (35)	298 (27)	1.5	1.5	1.3-1.8	<0.001

* Odds ratios are adjusted for service type, rank and age (< 20, 20-24, 25 to 34, ≥ 35 years), education and marital status.

Table 9.5 Prevalence and ORs of the seventeen* symptoms most commonly reported by Army participants in the past month

Symptom	GWV 'Total Yes' n (%)	Comp grp 'Total Yes' n (%)	Crude OR	Adj OR†	95% CI	P value
Feeling unrefreshed after sleep	64 (74)	116 (68)	1.3	1.2	0.7-2.3	0.475
Fatigue	61 (70)	103 (60)	1.6	1.7	0.9-3.1	0.081
Sleeping difficulties	57 (66)	108 (63)	1.1	1.1	0.6-2.0	0.694
Headaches	55 (63)	97 (57)	1.3	1.3	0.8-2.3	0.332
Irritability / outbursts of anger	52 (60)	91 (53)	1.3	1.5	0.8-2.5	0.192
General muscle aches or pains	51 (61)	98 (57)	1.2	1.0	0.6-1.8	0.944
Low back pain	50 (58)	104 (60)	0.9	1.0	0.5-1.7	0.926
Forgetfulness	43 (50)	70 (41)	1.5	1.6	0.9-2.8	0.115
Stiffness in several joints	43 (49)	76 (44)	1.2	1.3	0.8-2.3	0.324
Flatulence or burping	42 (48)	75 (44)	1.2	1.3	0.8-2.3	0.313
Difficulty finding the right word	40 (47)	71 (41)	1.2	1.3	0.7-2.2	0.404
Loss of concentration	40 (46)	66 (38)	1.4	1.3	0.8-2.3	0.284
Avoiding doing things or situations	37 (43)	60 (35)	1.4	1.6	0.9-2.9	0.092
Pain, without swelling or redness, in several joints	37 (43)	67 (39)	1.2	1.3	0.7-2.2	0.429
Itchy or painful eyes	34 (39)	61 (36)	1.2	1.1	0.6-2.0	0.676
Rash or skin irritation	34 (39)	57 (33)	1.3	1.3	0.7-2.2	0.423
Indigestion	34 (39)	48 (28)	1.6	1.7	0.9-3.0	0.083

* 17 symptoms were listed because the prevalence of the last three symptoms were identical for Gulf War veterans.
† Odds ratios are adjusted for service type, rank and age (< 20, 20-24, 25 to 34, ≥ 35 years), education and marital status

Table 9.6 Prevalence and ORs of the fifteen symptoms most commonly reported by Air Force participants in the past month

Symptom	GWV 'Total Yes' n (%)	Comp grp 'Total Yes' n (%)	Crude OR	Adj OR*	95% CI	P value
Fatigue	65 (62)	149 (59)	1.1	1.1	0.7-1.9	0.607
Sleeping difficulties	62 (59)	117 (46)	1.7	1.6	1.0-2.5	0.066
Feeling unrefreshed after sleep	59 (56)	129 (51)	1.2	1.2	0.7-1.9	0.462
Headache	53 (50)	119 (47)	1.2	1.1	0.7-1.8	0.665
Low back pain	51 (49)	103 (41)	1.3	1.3	0.8-2.1	0.304
Irritability / outbursts of anger	49 (47)	101 (40)	1.3	1.4	0.8-2.2	0.202
Loss of concentration	40 (38)	70 (28)	1.6	1.7	1.0-2.9	0.043
General muscle aches or pains	40 (38)	95 (38)	1.0	0.9	0.6-1.6	0.821
Difficulty finding the right word	38 (36)	85 (34)	1.1	0.9	0.6-1.5	0.766
Flatulence or burping	37 (35)	105 (42)	0.8	0.7	0.4-1.2	0.163
Stiffness in several joints	33 (31)	59 (23)	1.5	1.3	0.8-2.3	0.315
Sore throat	32 (30)	63 (25)	1.3	1.2	0.7-2.1	0.462
Rash or skin irritation	31 (30)	52 (21)	1.6	1.5	0.9-2.7	0.117
Itchy or painful eyes	30 (29)	65 (26)	1.2	1.1	0.7-1.9	0.639
Indigestion	30 (29)	58 (23)	1.3	1.3	0.8-2.3	0.308

* Odds ratios are adjusted for service type, rank and age (< 20, 20-24, 25 to 34, ≥35 years), education and marital status.

9.4.1.2 Total number of self-reported symptoms

The total number of symptoms reported by Gulf War veterans and the comparison group are shown in Table 9.7. Gulf War veterans were more likely than the comparison group to report a greater number of symptoms (>15) than the comparison group.

Table 9.7 Proportion of subjects with multiple self-reported symptoms

Number of symptoms reported	Gulf War veterans n (%)	Comparison group n (%)
0	43 (3)	83 (5)
1-5	271 (19)	392 (25)
6-10	303 (21)	397 (26)
11-15	241 (17)	280 (18)
16-20	209 (15)	158 (10)
21-30	213 (15)	165 (11)
>30	141 (10)	69 (4)

The mean total number of self-reported symptoms was used as a summary measure of health symptoms that were self-reported by the study groups. Table 9.8 shows that the mean total

number of symptoms reported by Gulf War veterans was 31 percent higher than for the comparison group overall, and was also greater for Gulf War veterans when the study groups were compared within subgroups of service type, rank and age. The mean total number of symptoms increased with age in the comparison group, but not in the Gulf War group. The difference between the Gulf War veterans and the comparison group in the mean total number of self-reported symptoms was greater in the younger age group (<20 years) and this difference decreased with age, approaching statistical significance across all the age groups (P=0.063). The differences between Gulf War veterans and the comparison group in the mean total number of self-reported symptoms tended to be greater in the 'other ranks-non supervisory', than in the 'officer' or 'other ranks – supervisory'. However, the mean total number of symptoms was not statistically significantly different across subgroups of rank (P=0.087) or service type (P=0.164).

Table 9.8 Total number of self-reported symptoms

	Total number of symptoms				
	Gulf War veterans	**Comparison group**	**Crude ratio of means**	**Adjusted ratio of means (95% CI) ***	**P value**
	Mean (SD)	**Mean (SD)**			
Total study population	14.7 (11.1)	11.3 (9.2)	1.3	1.3 (1.2-1.4)	<0.001
					P value for interaction†
Service type					
Navy	14.9 (11.2)	11.2 (9.3)	1.3	1.3 (1.3-1.4)	
Army	16.6 (11.6)	14.1 (9.8)	1.2	1.1 (1.0-1.4)	0.164
Air Force	11.4 (9.7)	9.5 (8.0)	1.2	1.2 (1.0-1.5)	
Rank					
Officer	11.0 (8.5)	8.8 (7.9)	1.3	1.3 (1.1-1.5)	
Other ranks - supervisory	15.1 (11.2)	12.5 (9.4)	1.2	1.3 (1.2-1.4)	0.087
Other ranks – non-supervisory	16.3 (11.9)	11.4 (9.6)	1.5	1.5 (1.3-1.6)	
Age					
<20 years	16.2 (11.7)	9.8 (8.6)	1.7	1.6 (1.4-2.0)	
20 - <25 years	14.5 (11.1)	10.8 (9.1)	1.3	1.3 (1.2-1.5)	
25 - <35 years	14.9 (10.9)	11.2 (8.7)	1.3	1.3 (1.2-1.4)	0.063
≥ 35 years	14.9 (11.5)	13.0 (10.9)	1.2	1.2 (1.0-1.4)	

* Ratio of means are adjusted for service type, rank, age (< 20, 20-24, 25 to 34, ≥35 years), education and marital status by negative binomial regression.
† P values shown for service type, rank and age result from a test of whether the ratio of the meant total number of symptoms between Gulf War veterans and comparison group are the same at each level of service type, rank or age.

9.4.2 Medical conditions

9.4.2.1 Self-reported medical conditions first diagnosed in 1991 or later

Self-reported medical conditions first diagnosed in 1991 or later, and those that were first diagnosed in 1991 or later and were rated as a 'possible' or 'probable' diagnosis by a HSA

doctor are shown in Table 9.9. The rating of the self-reported medical conditions by a HSA doctor as a 'possible' or 'probable' diagnosis was used to increase the accuracy of the self-reported medical conditions. The results of these latter analyses (right hand columns of Table 9.9 and bottom row of Table 9.13) included only those participants who completed a medical assessment and could, therefore, have their self-reported medical conditions in the postal questionnaire assessed by a HSA doctor. The self-reported medical conditions of all participants who completed a postal questionnaire, whether they subsequently had a medical assessment of not, were included in the remainder of the relevant analyses.

The most commonly reported medical conditions were of the musculoskeletal system, skin and psychological conditions. Most medical conditions were reported more frequently by Gulf War veterans than the comparison group. However, the increased reporting was statistically significant only for about half the medical conditions, and these involved several different body systems including the skin, psychological, gastrointestinal, respiratory, eye, nervous or ear, nose and throat systems. The strongest association was for posttraumatic stress disorder. The low prevalences and the resulting imprecision for many conditions limited further interpretation. Adjusted odds ratios were not able to be calculated for these rare medical conditions.

When self-reported medical conditions that were rated as a 'possible' or 'probable' condition were considered, the proportions of both groups reporting medical conditions decreased by a small amount. Most of the adjusted odds ratios were similar, suggesting that the proportions of medical conditions assessed by the doctors as 'non-medical' or 'unlikely' were similar between the two groups.

The differences between the Gulf War veteran and comparison groups in reporting of medical conditions (Figure 9.2) are less marked than the difference in the reporting of symptoms between the study groups that was illustrated in Figure 9.1.

Figure 9.2 Medical conditions first diagnosed in 1991 or later, with a prevalence of more than 2%, by study group

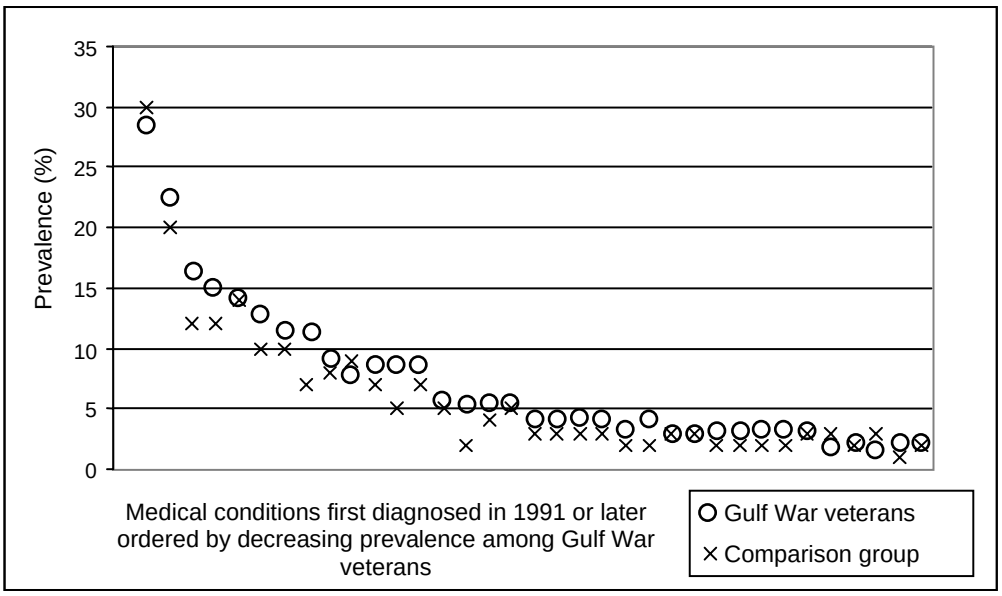


Table 9.9 Prevalence and ORs of self-reported doctor diagnosed or treated medical conditions first diagnosed in 1991 or later

Medical Condition	First diagnosed in 1991 or later						First diagnosed in 1991 or later and rated as a 'possible or probable' diagnosis**			
	GWV n (%)	Comp grp n (%)	Crude OR	Adj OR*	95% CI	P value	GWV n (%)	Comp grp n (%)	Adj OR*	95% CI
Back or neck problems	353 (29)	370 (30)	1.0	1.0	0.8-1.2	0.979	307 (26)	294 (27)	1.0	0.8-1.2
Joint problems	279 (22)	262 (20)	1.2	1.2	1.0-1.5	0.057	245 (20)	222 (179	1.1	0.9-1.4
Any other skin problem§	207 (16)	172 (12)	1.3	1.4	1.1-1.7	0.005	176 (14)	141 (11)	1.3	1.1-1.7
Anxiety, stress or depression	203 (15)	184 (12)	1.2	1.3	1.0-1.6	0.023	177 (13)	155 (12)	1.2	1.0-1.5
Hearing loss	185 (14)	201 (14)	1.0	1.0	0.8-1.2	0.944	170 (13)	172 (14)	1.0	0.8-1.2
Eye or vision problems eg. glaucoma	165 (13)	137 (10)	1.3	1.4	1.1-1.7	0.016	145 (11)	108 (9)	1.4	1.2-1.8
Bowel disorder eg. diarrhoea, constipation, bleeding	153 (11)	142 (10)	1.2	1.1	0.9-1.4	0.354	131 (10)	121 (10)	1.1	0.8-1.4
Sinus problems	136 (11)	100 (7)	1.5	1.5	1.1-2.0	0.005	122 (10)	81 (7)	1.5	1.1-2.0
High blood pressure	127 (9)	120 (8)	1.1	1.2	0.9-1.6	0.204	105 (8)	96 (7)	1.2	0.9-1.6
Other skin cancer eg. squamous cell or basal cell skin cancers	103 (8)	137 (9)	0.8	0.9	0.7-1.2	0.479	92 (7)	110 (8)	1.0	0.7-1.3
Ear infection	102 (8)	98 (7)	1.1	1.1	0.8-1.5	0.471	96 (8)	88 (7)	1.1	0.8-1.5
Dermatitis	102 (8)	66 (5)	1.8	1.7	1.2-2.4	0.001	87 (7)	52 (4)	1.8	1.3-2.6
Hayfever	102 (8)	89 (7)	1.3	1.3	1.0-1.8	0.070	84 (7)	75 (6)	1.2	0.8-1.7
Other psychiatric or psychological condition needing treatment or counselling¶	75 (5)	79 (5)	1.0	1.0	0.7-1.4	0.904	57 (4)	64 (5)	0.9	0.6-1.3
Post Traumatic Stress Disorder	70 (5)	31 (2)	2.5	3.1	2.0-4.9	<0.001	61 (4)	24 (2)	3.4	2.0-5.6
Migraines	68 (5)	51 (4)	1.5	1.4	1.0-2.1	0.077	61 (5)	41 (3)	1.5	1.0-2.2
Arthritis or rheumatism	67 (5)	76 (5)	0.9	1.0	0.7-1.4	0.853	63 (5)	64 (5)	1.0	0.7-1.4
Stomach or duodenal ulcers	62 (4)	43 (3)	1.6	1.6	1.1-2.5	0.015	58 (4)	37 (3)	1.6	1.1-2.75
Asthma	56 (4)	48 (3)	1.3	1.2	0.8-1.8	0.367	53 (4)	42 (3)	1.2	0.8-1.8
Sleep apnoea	52 (4)	42 (3)	1.4	1.4	0.9-2.1	0.125	33 (2)	31 (2)	1.1	0.6-1.8
Any disease of the hair or scalp, including hair loss	50 (4)	43 (3)	1.3	1.3	0.8-1.9	0.286	39 (3)	30 (2)	1.3	0.8-2.1

Medical Condition	First diagnosed in 1991 or later						First diagnosed in 1991 or later and rated as a 'possible or probable' diagnosis**			
	GWV n (%)	Comp grp n (%)	Crude OR	Adj OR*	95% CI	P value	GWV n (%)	Comp grp n (%)	Adj OR*	95% CI
Irritable bowel syndrome	48 (3)	27 (2)	1.2	2.1	1.3-3.5	0.002	42 (3)	19 (1)	2.4	1.4-4.3
Bronchitis	48 (4)	31 (2)	1.7	1.9	1.2-3.0	0.009	47 (4)	27 (2)	1.9	1.2-3.1
Any significant infections eg. hepatitis, HIV, pneumonia, glandular fever, leishmaniasis	44 (3)	43 (3)	1.1	1.1	0.7-1.7	0.610	41 (3)	34 (3)	1.2	0.8-2.0
Any disease of the genital organs	43 (3)	44 (3)	1.0	0.9	0.6-1.5	0.774	36 (3)	37 (3)	0.8	0.5-1.3
Alcohol abuse or dependency	42 (3)	24 (2)	1.9	1.9	1.1-3.2	0.019	36 (3)	20 (1)	1.7	0.9-3.0
Sexual problems	42 (3)	33 (2)	1.4	1.6	1.0-2.6	0.058	29 (2)	24 (2)	1.4	0.8-2.5
Eczema	39 (3)	29 (2)	1.5	1.5	0.9-2.4	0.115	36 (3)	24 (2)	1.5	0.9-2.6
Psoriasis	36 (3)	30 (2)	1.4	1.3	0.8-2.1	0.371	28 (2)	27 (2)	1.0	0.6-1.7
Any other kind of cancer, tumour or malignancy	35 (3)	45 (3)	0.8	0.9	0.5-1.4	0.514	34 (3)	40 (3)	0.9	0.5-1.4
Heart disease or condition	33 (2)	42 (3)	0.9	0.8	0.5-1.3	0.448	23 (2)	34 (3)	0.7	0.4-1.1
Kidney disease eg. stones, infection, bleeding	32 (2)	35 (2)	1.0	1.1	0.6-1.7	0.842	30 (2)	30 (2)	1.1	0.6-1.8
Pneumonia	30 (2)	47 (3)	0.7	0.7	0.4-1.1	0.090	28 (2)	42 (3)	0.6	0.4-1.1
Low fertility	30 (2)	20 (1)	1.6	1.5	0.8-2.6	0.195	27 (2)	15 (1)	1.6	0.9-3.1
Incontinence or difficulty passing urine	27 (2)	30 (2)	1.0	1.1	0.6-1.8	0.816	18 (1)	27 (2)	0.7	0.4-1.3
Blood disorder; eg. anaemia	20 (1)	17 (1)	1.3	1.4	0.7-2.6	0.371	13 (1)	13 (1)	1.1	0.5-2.3
Bladder disease eg. infection, bleeding	18 (1)	17 (1)	1.2	1.2	0.6-2.3	0.677	16 (1)	12 (1)	1.4	0.6-2.9
Malignant melanoma	18 (1)	20 (1)	1.0	1.0	0.5-1.9	0.981	14 (1)	11 (1)	1.3	0.6-3.0
Drug abuse or dependency	17 (1)	3 (<1)	6.2	5.6†	1.6-30.1	0.003	17 (1)	3 (<1)	5.0†	1.4-26.8
Hepatitis or yellow jaundice	14 (1)	12 (1)	1.3	1.3	0.6-3.0	0.520	13 (1)	10 (1)	1.3	0.5-3.2
Diabetes	14 (1)	22 (1)	0.7	0.7	0.4-1.5	0.364	13 (1)	21 (1)	0.6	0.3-1.3
Chronic Fatigue Syndrome	13 (1)	17 (1)	0.8	0.8	0.4-1.7	0.608	10 (1)	9 (1)	1.2	0.5-2.9
Food allergy	13 (1)	17 (1)	0.8	0.8	0.4-1.6	0.520	10 (1)	12 (1)	0.7	0.3-1.7
Colitis / Crohn's disease	11 (1)	6 (<1)	2.0	2.1	0.8-5.8	0.157	11 (1)	5 (<1)	2.1†	0.7-7.8
Malaria	8 (1)	9 (1)	1.0	1.2	0.4-3.1	0.749	8 (1)	4 (<1)	2.7†	0.7-12.6

Medical Condition	First diagnosed in 1991 or later						First diagnosed in 1991 or later and rated as a 'possible or probable' diagnosis**			
	GWV n (%)	Comp grp n (%)	Crude OR	Adj OR*	95% CI	P value	GWV n (%)	Comp grp n (%)	Adj OR*	95% CI
Yeast disease or candidiasis	8 (1)	9 (1)	1.0	0.8	0.3-2.3	0.712	6 (<1)	5 (<1)	1.5†	0.3-6.0
Other lung disease, eg. emphysema	7 (1)	7 (1)	1.2	1.0	0.4-3.0	0.975	5 (<1)	6 (<1)	0.8†	0.2-3.1
A thyroid problem	7 (1)	9 (1)	0.8	1.0	0.4-2.8	0.972	7 (1)	9 (1)	1.0†	0.3-2.9
Multiple chemical sensitivity or environmental illness	6 (<1)	5 (<1)	1.3	1.3†	0.3-5.1	0.989	4 (<1)	3 (<1)	1.3†	0.2-7.8
Tuberculosis (TB)	5 (<1)	3 (<1)	1.8	2.2†	0.4-14.5	0.483	3 (<1)	3 (<1)	1.4†	0.2-9.8
Epilepsy	4 (<1)	1 (<1)	4.4	3.6†	0.4-177	0.449	4 (<1)	1 (<1)	3.6†	0.3-164
Fibrositis or fibromyalgia	4 (<1)	0 (0)	inf‡	inf‡	0.9-inf	0.067	2 (<1)	0 (0)	inf‡	0.3-inf
Stroke	3 (<1)	3 (<1)	1.1	1.0†	0.1-8.0	1.000	3 (<1)	3 (<1)	1.0†	0.1-7.4
Motor neurone disease	2 (<1)	1 (<1)	2.2	3.7†	0.2-220	0.581	2 (<1)	1 (<1)	3.7†	0.2-198
Narcolepsy	2 (<1)	2 (<1)	1.1	1.7†	0.1-24.8	1.000	1 (<1)	2 (<1)	0.6†	0.0-12.6
Multiple sclerosis	1 (<1)	3 (<1)	0.4	0.3†	0.0-3.5	0.491	1 (<1)	2 (<1)	0.4†	0.0-7.6
Cirrhosis of the liver	1 (<1)	0 (0)	inf‡	inf‡	0.0-inf	0.988	1 (<1)	0 (0)	inf‡	0.0-inf
Sick building syndrome	1 (<1)	3 (<1)	0.4	0.3†	0.0-4.4	0.641	0 (0)	2 (<1)	0.0†	0.0-6.6

* Odds ratios are adjusted for service type, rank and age (< 20, 20-24, 25 to 34, ≥35 years), education and marital status
† Odds ratios are adjusted for service type, rank and age (<25 vs ≥25 years). Confidence intervals and P values for adjusted odds ratios were obtained using exact methods for stratified 2x2 tables
‡ inf=infinity (undefined)
§ 'Other skin problem' refers to skin conditions other than dermatitis, eczema, psoriasis, malignant melanoma or other skin cancer as reported by the participant in the postal questionnaire.
¶ 'Other psychiatric or psychological condition needing treatment or counselling' refers to psychiatric or psychological conditions other than alcohol abuse or dependency, drug abuse or dependency, anxiety stress or depression, or posttraumatic stress disorder as reported by the participant in the postal questionnaire.
** Includes only those participants who completed a medical assessment and could, therefore, have their self-reported medical condition in the postal questionnaire assessed by a HSA doctor.

9.4.2.2 Comparison by service type

Table 9.10, Table 9.11 and Table 9.12 show the self-reported doctor diagnosed or treated medical conditions first diagnosed in 1991 or later that were most commonly reported within each of the service types. Some conditions such as back or neck problems, joint problems, any other skin problems, hearing loss, anxiety stress or depression, eye or vision problems, bowel disorder, and sinus problems were consistently reported by all service types in their ten most commonly reported conditions. Other medical conditions were reported in the top ten for only some of the service types. These included ear infection in the Navy, but not in the Army or Air Force subgroups; posttraumatic stress disorder in the Army; hay fever and other skin cancer in the Air Force and high blood pressure in the Navy and Army, but not the other service types respectively.

Although the proportions of Gulf War veterans in the service subgroups reporting medical conditions with an onset in 1991 or later were greater than their comparison groups for most of the medical conditions (except eye or vision problems in the Army and Air Force, and any other skin problem in the Air Force) the differences are significant for only some of the conditions. The odds ratios differ significantly across the services for only one medical condition, eye or vision problems (p=0.024).

Table 9.10 Prevalence and ORs of the ten most commonly self-reported doctor diagnosed or treated medical conditions first diagnosed in 1991 or later reported by Navy participants

Medical Condition	GWV n (%)	Comp grp n (%)	Crude OR	Adj OR*	95% CI	P value
Back or neck problems	299 (28)	266 (29)	1.0	1.0	0.8-1.2	0.942
Joint problems	244 (22)	186 (19)	1.2	1.2	1.0-1.5	0.050
Any other skin problem	177 (16)	119 (12)	1.4	1.4	1.1-1.8	0.007
Hearing loss	162 (14)	151 (15)	1.0	1.0	0.8-1.3	0.975
Anxiety, stress or depression	171 (14)	135 (12)	1.2	1.3	1.0-1.6	0.058
Eye or vision problems (eg glaucoma)	147 (13)	87 (9)	1.6	1.6	1.2-2.1	0.001
Bowel disorder (eg diarrhoea, constipation, bleeding)	130 (11)	111 (11)	1.0	1.1	0.8-1.4	0.698
Sinus problems	114 (10)	76 (8)	1.4	1.4	1.0-1.9	0.031
High blood pressure	103 (9)	85 (8)	1.1	1.1	0.8-1.5	0.411
Ear infection	92 (9)	67 (7)	1.3	1.2	0.9-1.7	0.218

* Odds ratios are adjusted for rank, age (< 20, 20-24, 25 to 34, ≥35 years), education and marital status.

Table 9.11 Prevalence and ORs of the ten self-reported doctor diagnosed or treated medical conditions first diagnosed in 1991 or later most commonly reported by Army participants

Medical Condition	GWV n (%)	Comp grp n (%)	Crude OR	Adj OR*	95% CI	P value
Back or neck problems	27 (40)	47 (40)	1.0	1.1	0.6-2.1	0.785
Joint problems	20 (34)	42 (33)	1.0	1.1	0.6-2.2	0.773
Any other skin problem	17 (23)	20 (14)	1.9	2.0	1.0-4.3	0.063
Anxiety, stress or depression	19 (23)	20 (12)	2.1	2.1	1.0-4.4	0.036
High blood pressure	15 (17)	15 (9)	2.1	2.0	0.9-4.6	0.102
Bowel disorder (eg diarrhoea, constipation, bleeding)	12 (15)	13 (8)	1.9	2.6	1.1-6.5	0.037
Sinus problems	11 (15)	7 (5)	3.4	3.4	1.2-9.9	0.023
Hearing loss	11 (15)	23 (15)	0.9	0.9	0.4-1.9	0.711
Post Traumatic Stress Disorder	12 (14)	8 (5)	3.3	4.1	1.5-11.5	0.007
Eye or vision problems (eg glaucoma)	9 (12)	25 (17)	0.7	0.6	0.3-1.5	0.265

* Odds ratios are adjusted for rank, age (< 20, 20-24, 25 to 34, ≥35 years), education and marital status

Table 9.12 Prevalence and ORs of the ten self-reported doctor diagnosed or treated medical conditions first diagnosed in 1991 or later most commonly reported by Air Force participants

Medical Condition	GWV n (%)	Comp grp n (%)	Crude OR	Adj OR*	95% CI	P value
Back or neck problems	27 (33)	57 (30)	1.2	1.1	0.6-1.9	0.799
Joint problems	15 (17)	34 (15)	1.1	1.0	0.5-2.0	0.946
Other skin cancer (eg squamous cell or basal cell skin cancers)	15 (15)	31 (13)	1.2	1.1	0.6-2.2	0.787
Any other skin problem	13 (13)	33 (15)	0.9	0.8	0.4-1.8	0.656
Hearing loss	12 (13)	27 (12)	1.1	0.9	0.4-1.9	0.751
Anxiety, stress or depression	13 (12)	29 (12)	1.1	1.1	0.5-2.3	0.870
Sinus problems	11 (12)	17 (8)	1.6	1.1	0.5-2.7	0.784
Bowel disorder (eg diarrhoea, constipation, bleeding)	11 (11)	18 (8)	1.5	1.3	0.5-2.9	0.596
Hayfever	8 (9)	17 (8)	1.1	1.2	0.5-3.1	0.680
Eye or vision problems (eg glaucoma)	9 (9)	25 (11)	0.8	0.8	0.3-1.9	0.583

* Odds ratios are adjusted for rank, age (< 20, 20-24, 25 to 34, ≥35 years), education and marital status.

9.4.2.3 Total number of self-reported medical conditions

One thousand one hundred and thirty-six (80%) Gulf War veterans reported at least one, and 146 (10%) reported more than five, medical conditions that had been first diagnosed in 1991 or later. One thousand one hundred and eighty-six (77%) comparison group subjects reported at least one, and 99 (6%) reported more than five, medical conditions that had been first diagnosed in 1991 or later (data not tabulated).

Gulf War veterans reported a maximum of 22, and the comparison group a maximum of 13, medical conditions first diagnosed in 1991 or later. Gulf War veterans reported a maximum of 21, and the comparison group a maximum of 11, medical conditions first diagnosed in 1991 and rated as a 'possible' or 'probable' diagnosis by a HSA doctor (data not tabulated).

The mean total number of self-reported medical conditions was used as a summary measure to compare the reporting of medical conditions between the study groups, and these are shown in Table 9.13. Gulf War veterans reported an increased mean total number of self-reported medical conditions than the comparison group. This was regardless of whether these conditions were first diagnosed in 1991 or since, or whether the conditions were first diagnosed in 1991 or since and had been rated as a 'possible' or 'probable' diagnosis by a HSA doctor and were thus considered to be more accurate diagnoses. Gulf War veterans reported 20% more medical conditions first diagnosed in 1991 or later and 17% more 'possible' or 'probable' medical conditions first diagnosed in 1991 or later.

Table 9.13 Mean total number of self-reported medical conditions

	Mean total number of medical conditions				
	Gulf War veterans	**Comparison group**	**Crude ratio of means**	**Adjusted ratio of means * (95% CI)**	**P value**
	Mean (SD)	**Mean (SD)**			
First diagnosed in 1991 or later	2.4 (2.4)	2.0 (2.0)	1.2	1.2 (1.1-1.3)	<0.001
'Possible' or 'probable' medical conditions first diagnosed in 1991 or later †	2.2 (2.2)	1.9 (1.8)	1.1	1.2 (1.1-1.3)	<0.001

* Ratios of means are adjusted for service type, rank and age (< 20, 20-24, 25 to 34, ≥35 years), education and marital status by negative binomial regression

† Includes only those participants who completed a medical assessment and could, therefore, have their self-reported medical condition in the postal questionnaire assessed by a HSA doctor.

9.4.2.4 Doctor's assessment of the likelihood of self-reported medical conditions

One thousand and ninety-four Gulf War veterans and 1043 comparison group subjects reported 3265 and 2770 medical conditions respectively, which were subsequently assessed by the HSA doctors for the likelihood of the diagnosis. The results are shown in Table 9.14. These results excluded 351 medical conditions reported by 209 subjects who did not attend for a HSA medical assessment and 214 medical conditions reported by 132 subjects who did attend for a HSA medical assessment but for which the doctor's assessment was missing.

Table 9.14 HSA doctors' assessment of the likelihood of self-reported medical conditions that were first diagnosed in 1991 or later

HSA doctor's assessment of the diagnosis	Gulf War veterans Number of medical conditions (%)	Comparison group Number of medical conditions (%)	P value†
Non-medical	165 (5.1)	98 (3.5)	
Unlikely	119 (3.6)	87 (3.1)	
Possible	528 (16.2)	418 (15.1)	0.016
Probable	2453 (75.1)	2167 (78.2)	

* n=number of medical conditions

† The P value is for an ordered table of all non-missing values, ie excluding doctor's assessment code missing, adjusting for clustering arising from multiple self-reported diagnoses within the same individual.

For the Gulf War veteran group, 2981 out of 3265 (91.3%) medical conditions were assessed as 'possible' or 'probable' diagnoses, and for the comparison group 2585 out of 2770 (93.3%) medical conditions were assessed as 'possible' or 'probable'. Less than 10% of the diagnoses in both study groups were assessed as a 'non-medical' or 'unlikely' diagnoses. This proportion was slightly greater in the Gulf War veteran group (8.7% vs 6.6%).

9.4.2.5 Self-reported doctor medical conditions first diagnosed in 1990 or earlier

Self-reported medical conditions first diagnosed in 1991 or later are of prime interest in this study in relation to Gulf War deployment. Self-reported medical conditions first diagnosed in 1990 or earlier, ie medical conditions defined in this study as having an onset prior to the Gulf War were also compared to estimate differences in pre-Gulf War morbidity between the two study groups (data not tabulated).

The comparison group reported many conditions that were first diagnosed in 1990 or earlier more commonly than the Gulf war veterans. These self-reported medical conditions included high blood pressure, heart disease, migraines, infections such as pneumonia, hepatitis, or other significant infections, kidney, bladder and bowel disorders, back, neck and joint problems, ear infections, hearing loss, almost all skin diseases other than dermatitis or eczema, some psychological conditions such as anxiety, stress or depression, hay fever, food allergy, diseases of the genital organs, and low fertility. The difference in prevalence ranged from 0.4% for heart disease to 5.0% for back or neck problems.

There were few conditions, such as dermatitis or eczema, skin cancers other than malignant melanoma, and asthma for which the proportion of Gulf War veterans reporting the medical conditions was greater than the comparison group.

Many of the self-reported medical conditions first diagnosed in 1990 or earlier were of low prevalence in both study groups. Some other medical conditions, such as bowel disorder, any significant infections, back, neck or joint problems, ear infection, hearing loss, some skin problems, hayfever, and any diseases of the genital organ had a prevalence greater than 5% in at least one of the study groups.

Therefore these findings suggests that pre-Gulf war, both study groups were very healthy, but that the comparison group was reportedly a little healthier than the Gulf War group.

9.4.3 Hospitalisations, functional impairment due to illness or injury, and current use of medication

The results of the assessment of hospitalisations during the past twelve months, functional impairment due to illness or injury, and current use of medication are shown in Table 9.15.

The pattern of the number of days of hospitalisations, reported by the two study groups, was very similar. The median number of days hospitalised in the last 12 months was three days for Gulf War veterans (range 1-70) and two days (range 1-240) for the comparison group. If the one comparison group subject who reported spending 240 days in hospital during the past year was excluded, the ranges for days in hospital were similar for the Gulf War veterans and comparison group (1-70 days vs 1-86 days in hospital).

The mean (SD) number of days hospitalised for Gulf War veterans 0.14 (0.45) days was similar to that of the comparison group 0.13 (0.43) days. The crude ratio of the mean number of hospitalisations was 1.07. Adjustment for possible confounders made little difference, and the adjusted ratio of means of 1.11 (95% CI 0.87-1.42) was not statistically significant (P=0.407).

A significantly greater proportion of Gulf War veterans reported functional impairment over the past two weeks (21% vs 17%). The proportions of Gulf War veterans and comparison group reporting current use of medication (35% vs 33%) were similar.

Table 9.15 Hospitalisation during the past 12 months, functional impairment during the past 2 weeks, and current use of any medication

	GWV n (%)	Comp grp n (%)	Crude OR	Adj OR*	95% CI	P value
Hospitalisations						
None	1269 (89.4)	1383 (89.9)				
1 hospitalisation	114 (8.0)	126 (8.2)				
2 hospitalisations	28 (2.0)	21 (1.4)				
3 hospitalisations	6 (0.4)	6 (0.4)				
4 hospitalisations	2 (0.1)	3 (0.2)				
Any hospitalisation	150 (10.6)	156 (10.1)	1.1	1.3	0.8-1.3	0.793
Functional impairment						
Total number who stayed at home	295 (20.8)	256 (16.6)	1.3	1.3	1.1-1.6	0.004
Medication use						
Current use of any kind of medication	493 (35.0)	515 (33.4)	1.1	1.1	1.0-1.3	0.144

* Odds ratios are adjusted for service type, rank and age (< 20, 20-24, 25 to 34, ≥35 years), education and marital status by negative binomial regression

9.4.4 SF-12 Health Survey

Figure 9.3 and Figure 9.4 show the distributions of the PCS-12 and MCS-12 in Gulf War veterans and comparison groups, which are both skewed to the left. The differences in distributions between the groups were more marked for the MCS-12.

Figure 9.3 Distributions of the PCS-12 score of the SF-12 Health Survey

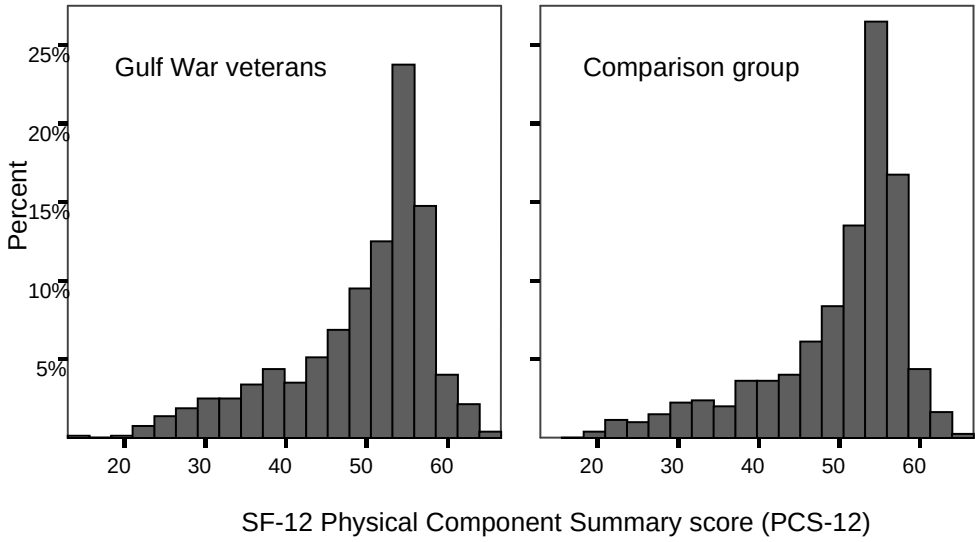


Figure 9.4 Distributions of the MCS-12 score of the SF-12 Health Survey

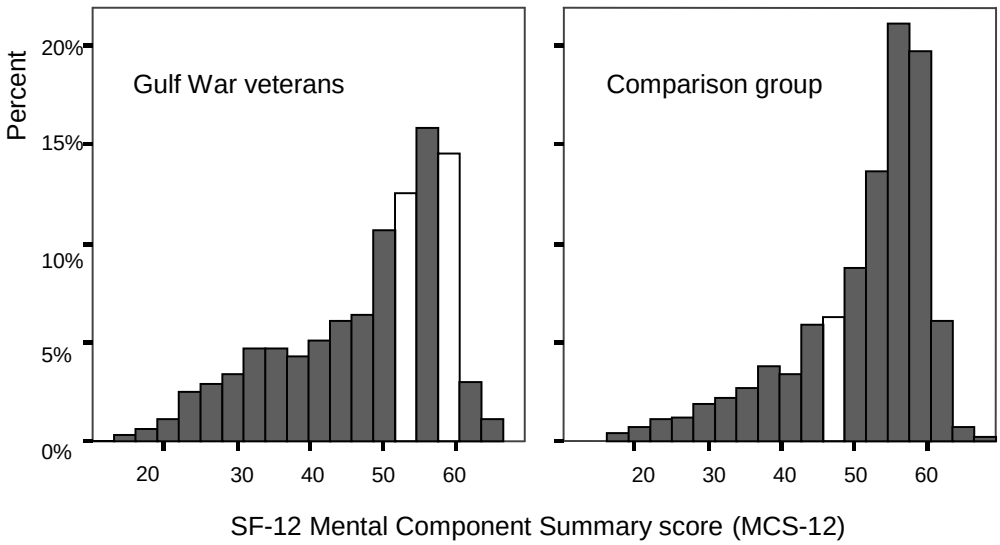


Table 9.16 shows the mean scores of the PCS-12 and the MCS-12 for the total study population and the service subgroups. Across the total study population and within the Navy subgroup, Gulf War veterans recorded poorer physical health and mental health scores. Army subjects in both groups scored more poorly on both the PCS-12 and the MCS-12 compared with the Navy and Air Force subjects, with mean scores below the US population mean of 50. Army Gulf War veterans recorded significantly poorer MCS-12 scores than the comparison group. Analyses using median scores provided very similar results.

Table 9.16 Mean PCS-12 and MCS-12 scores of the SF-12 Health Survey

	SF-12 score				
	GWV	**Comparison group**	**Crude difference between means**	**Adjusted difference* (95% CI)**	**P value**
Total study population					
PCS-12 mean (SD)	49.2 (9.2)	49.9 (9.0)	-0.7	-0.9 (-1.6, -0.2)	0.008
MCS-12 mean (SD)	47.4 (11.2)	50.9 (9.5)	-3.5	-3.4 (-4.2, -2.6)	<0.001
Navy					
PCS-12 mean (SD)	49.2 (9.0)	50.0 (8.6)	-0.8	-1.0 (-1.7, -0.3)	0.006
MCS-12 mean (SD)	47.3 (11.1)	51.0 (9.4)	-3.7	-3.7 (-4.5, -2.8)	<0.001
Army					
PCS-12 mean (SD)	47.6 (10.6)	45.9 (11.7)	1.7	0.9 (-2.1, 3.9)	0.554
MCS-12 mean (SD)	45.6 (12.4)	49.9 (10.6)	-4.3	-4.2 (-7.2, -1.2)	0.006
Air Force					
PCS-12 mean (SD)	50.4 (9.8)	52.4 (7.7)	-2.0	-1.8 (-3.8, 0.2)	0.084
MCS-12 mean (SD)	50.3 (10.9)	51.1 (9.4)	-0.8	-0.5 (-2.8, 1.9)	0.706

* Difference between means are adjusted for service type, rank and age (< 20, 20-24, 25 to 34, ≥35 years), education and marital status by linear regression.

Additional analyses (data not tabulated) indicated that the MCS-12 results differed by rank. The difference in mean MCS-12 scores between the Gulf War veteran and comparison groups was greatest for the 'other ranks – non supervisory' subgroup, where the difference (-5.3) was about twice as great as the differences in means for the 'officer' (-2.5) and 'other ranks – supervisory' (-2.6) subgroups (P value for interaction =0.006). Similarly, the MCS-12 results differed by age group, with differences in MCS-12 means between Gulf War veterans and comparison group of -7.1 for age <20 years and -1.9 for age ≥35 years (p=0.004). The linear decrease in group differences with age was significant (p=0.024). The differences in mean MCS-12 scores between the Gulf War veteran and comparison groups by service type were less marked. The difference in means for the Army (-4.3), Navy (-3.7) and Air Force (-0.8) were not statistically significantly different (P=0.069) across the service subgroups. The PCS-12 results did not differ for the subgroups in the comparison of Gulf War and comparison groups.

To compare the proportions of subjects with very low SF-12 scores, the proportion of Gulf War veterans and comparison group subjects in our study who fell below the US 25th percentile of the SF-12 score were compared. This analysis extended the approach of a previous study of Gulf War veterans,[249] and the results are shown in Table 9.17. A significantly greater proportion of Gulf War veterans have PCS-12 and MCS-12 scores that are lower than the 25th percentile for the US population norms than the comparison group (Table 9.17). A significantly greater proportion of Navy (adjusted OR 2.0) and Army (adjusted OR 2.2), but not Air Force (adjusted OR 0.9) Gulf War veterans have an MCS-12 score that was lower than the 25th percentile than the comparison group (P value for interaction =0.045). The decreasing odds ratio for MCS-12 with increasing age (p=0.046), with a decrease in odds ratios of OR=3.1 for age <20 years to OR=1.4 for age ≥35 years,

indicted greater risk of poorer mental health in younger Gulf War veterans. No similar age or service type patterns emerged for the PCS-12.

Table 9.17 Proportion of participants with SF-12 scale scores less than the 25th percentile of the US population norms

	Scores below US 25th percentile*				
	GWV n (%)	Comp grp n (%)	Crude OR	Adjusted OR† (95% CI)	P value
Total study population					
PCS-12	401 (29)	377 (25)	1.2	1.3 (1.1, 1.6)	0.001
MCS-12	476 (35)	338 (22)	1.8	1.9 (1.6, 2.2)	<0.001

* US 25th percentiles are 45.13 for MCS-12 and 46.53 for PCS-12.
† Odds ratios are adjusted for service type, rank and age (< 20, 20-24, 25 to 34, ≥ 35 years), education and marital status.

9.4.5 Physical measures of general health

9.4.5.1 Height, weight, body mass index, waist and hip circumference and waist-to-hip ratio

The mean height of both study groups was identical (Table 9.18). The mean weight, BMI, hip and waist circumferences of Gulf War veterans and the comparison group were very similar.

Table 9.18 Mean height, weight, BMI, hip and waist circumference

	GWV		Comp grp					
Parameter	mean	(SD)	mean	(SD)	Crude OR	Adj OR*	(95% CI)	P value
Height (metres)	1.78	(0.07)	1.78	(0.07)	-0.001	-0.001	(-0.006, 0.004)	0.730
Weight (kg)	88.6	(14.6)	89.5	(14.6)	-0.9	-1.1	(-2.2, -0.04)	0.043
BMI (kg / m^2)	28.1	(4.1)	28.3	(4.1)	-0.3	-0.3	(-0.6, 0.02)	0.036
Hip circumference (cm)	107.2	(8.1)	107.4	(8.1)	-0.2	-0.3	(-0.9, 0.3	0.300
Waist circumference (cm)	97.7	(10.7)	98.2	(10.7)	-0.5	-0.6	(-1.4, 0.2)	0.154

* Odds ratios are adjusted for service type, rank and age (< 20, 20-24, 25 to 34, ≥ 35 years), education and marital status

A breakdown of BMI into categories of underweight, normal range and overweight or obese are shown in Table 9.19. Very few participants of both groups were underweight, and the numbers were too small for further meaningful comparison. The proportion of Gulf War veterans whose BMI was within the normal range was similar to that in the comparison group. The proportion of Gulf War veterans whose BMI was within the overweight or obese range was similar to that of the comparison group. Within this category most Gulf War veterans were in the pre-obese or obese class 1 subcategories. Slightly more Gulf War veterans than the comparison group had a BMI in the obese class 3 subcategory.

Table 9.19 Prevalence and ORs of categories of BMI

BMI categories (kg/m^2)	GWV n (%)	Comp grp n (%)	Crude OR	Adj OR* (95% CI)	P value
Underweight (<18.50)	5 (0.4)	1 (0.1)	4.9	-	-
Normal range (18.5-<25.00)	294 (21.2)	287 (20.8)	1.0 (reference)*	-	-
18.5-<20.00	8 (0.6)	9 (0.7)	-	-	-
20.00-<25.00	286 (20.7)	278 (20.2)	-	-	-
Overweight or obese (≥25.00)	1085 (78.4)	1091 (79.1)	1.0	1.0 (0.8-1.2)	0.958
Pre-obese (25.00-<30.00)	714 (51.6)	669 (48.5)	-	-	-
Obese class 1 (30.00-<35.00)	298 (21.5)	332 (24.1)	-	-	-
Obese class 2 (35.00-<40.00)	55 (4.0)	78 (5.7)	-	-	-
Obese class 3 (≥40.00)	18 (1.3)	12 (0.9)	-	-	-

* Odds ratios are adjusted for service type, rank, age (< 20, 20-24, 25 to 34, ≥35 years), education and marital status
† Reference category is normal or underweight

A slightly greater proportion of Gulf War veterans had a waist circumference ≤94 cm and a slightly lower proportion of Gulf War veterans had a waist circumference >94cm or >102 cm than the comparison group (Table 9.20). When classified according to WHR >0.9, fewer Gulf War veterans exceeded this cutoff point. The difference was statistically significant, but not considered clinically important.

Table 9.20 Prevalence and ORs of categories of waist circumference and WHR

	Gulf War veterans n (%)	Comparison group n (%)	Crude OR	Adj OR*	95% CI	P value
Waist circumference (cm)						
≤ 94 cm	549 (39.7)	519 (37.7)	-	-	-	-
>94 cm	834 (60.3)	859 (62.3)	-	-	-	-
>102 cm	426 (43.7)	458 (46.9)	-	-	-	-
WHR						
>0.9	751 (52.7)	828 (53.5)	1.0	0.8	(0.7-0.9)	0.002

* Odds ratios are adjusted for service type, rank and age (< 20, 20-24, 25 to 34, ≥35 years), education and marital status

9.4.5.2 Blood pressure

The mean (SD) systolic blood pressures of Gulf War veteran and comparison group subjects {125.2 (12.6) vs 124.5 (12.5)} and mean (SD) diastolic blood pressures {80.6 (9.9) and 80.0 (9.9)} were very similar, and within the normal category.

Slightly more Gulf War veterans had elevated blood pressure than the comparison group for all categories except Grade 2 hypertension, but none of the differences between the groups were statistically significant (Table 9.21).

Table 9.21 Prevalence and ORs of blood pressure categories

Blood pressure categories (mmHg)	GWV n (%)	Comp grp n (%)	Crude OR	Adj OR†	95% CI	P value
Normal (systolic <130 and diastolic <85)	782 (57.0)	795 (58.1)		1.0		
Optimal (systolic <120 and diastolic <80)	315 (23.0)	385 (28.1)	-	-	-	-
High-normal (systolic 130-139 or diastolic 85-89)	292 (21.3)	280 (20.5)	1.1	1.1	0.9-1.3	0.514
Hypertension (systolic ≥140 and/or diastolic ≥90)	251 (18.3)	236 (17.3)	1.1	1.1	0.9-1.4	0.334
Grade 1 (systolic 140-159 or diastolic 90-99)	195 (14.2)	182 (13.3)	-	-	-	-
Grade 2 (systolic 160-179 or diastolic 100-109)	36 (2.6)	37 (2.7)	-	-	-	-
Grade 3 (systolic ≥180 or diastolic ≥110	20 (1.5)	17 (1.2)	-	-	-	-
Isolated systolic* (systolic ≥140 and diastolic <90)	46 (3.4)	57 (4.2)	0.8	0.8	0.5-1.2	0.284

* Isolated systolic hypertension could be further defined according as Grade 1, 2 or 3 isolated systolic hypertension
† Odds ratios are adjusted service type, rank and age (< 20, 20-24, 25 to 34, ≥35 years), education and marital status usuals by polytomous logistic regression with normal blood pressure as the reference category

9.4.5.3 Fitness test

Similar proportions, 1153 (83.6%) Gulf War veterans and 1142 (83.0%) of the comparison group, were considered fit to perform the step test. The remainder either voluntarily declined participation in the test or were assessed by a HSA doctor as being unfit to perform the test according to predetermined criteria. Of the 2295 who performed the test, 2258 had both pulse measurements recorded. Fifty-three (4.7%) of Gulf War veterans and 50 (4.5%) of the comparison group did not complete the full three minutes of the test. A reason, and sometimes more than one reason, for stopping was provided for these participants. These reasons included fatigue in 11 Gulf War veterans and 10 comparison group subjects, shortness of breath in 18 Gulf War veterans and 16 comparison group subjects, pain in 19 Gulf War veterans and 12 comparison group subjects and another reason in 8 Gulf War veterans and 14 comparison group subjects. Therefore, the frequency of, and reasons for, stopping the test were similar for each group.

Amongst those subjects who completed the test, the mean recovery heart rate was 139.4 (SD 17.6) beats per minute for Gulf War veterans and 137.9 (SD 18.1) beats per minute for the comparison group. The adjusted mean difference in heart rate on completion of the step test was slightly higher for Gulf War veterans than the comparison group but this difference was not statistically significant (p=0.140). The mean differences in heart rate for those who completed the test were grouped into tertiles representing 'high', 'medium' and 'low' fitness categories (Table 9.22), with the lower recovery heart rates representing a higher level of fitness. Gulf War veterans were slightly less likely to record recovery heart rates in the lowest tertile or 'higher fitness' category, but the difference was small and not statistically significant (odds ratio from ordinal logistic regression OR=0.9, 95%CI 0.8 to 1.1, p=0.390).

Table 9.22 Fitness categories according to mean difference in heart rate

Mean recovery heart rate, beats per minute (fitness category)	Gulf War veterans n (%)	Comparison group n (%)
59-131 (higher fitness)	352 (32.3)	384 (35.9)
132-147 (medium fitness)	381 (35.0)	349 (32.6)
148-193 (lower fitness)	356 (32.7)	337 (31.5)

9.4.6 Gulf War veteran group subanalysis

The following tables (Table 9.23, Table 9.24, Table 9.25, Table 9.26) present the analysis of Gulf War service related exposures in relation to those general health outcomes found to be higher in the Gulf War veteran group. These analyses were confined to Gulf War veterans only. The exposure metrics used in these analyses are explained in chapter 8.

Table 9.23 shows that the total number of self-reported general health symptoms in the past month was associated with several self-reported exposures including having at least ten immunisations, pyridostigmine bromide, anti-biological warfare tablets, pesticides/insecticides, repellents, being in a chemical weapons area and stressful military service experiences (MSE questionnaire score). There was no association with some other exposures such as 'any' immunisations, clustering of immunisations, antimalarials or depleted uranium (DU). Increasing numbers of stressful military service experiences during the Gulf War, represented by increasing MSE questionnaire scores, were associated with increasing total number of symptoms in a strong dose response relationship. A dose response relationship was also found for immunisations and symptom reporting, where the risk of symptom reporting increased after 10 or more immunisations were reported. A weak dose response relationship was found for taking pyridostigmine bromide tablets.

Table 9.23 Subanalysis of Gulf War veteran total number of general health symptoms by exposures and experiences

Gulf War exposure	Total number of general health symptoms						
	N	Mean	(SD)	Ratio of means	Adj ratio[¶]	CI	P value
Deployment completed before air war							
Yes	331	13.3	(10.0)	1.0	1.0	-	-
No	1089	15.1	(11.4)	1.1	1.1	1.0-1.2	0.051
Immunisations							
None	119	13.8	(11.1)	1.0	1.0	-	-
Any	956	14.0	(10.7)	1.0	1.0	0.9-1.2	0.895
1-4	267	11.6	(8.8)	0.8	0.9	0.7-1.0	
5-9	563	14.1	(10.8)	1.0	1.0	0.9-1.2	
10 or more	126	18.8	(12.4)	1.4	1.3	1.1-1.6	
Dose response in those ≥1[*]	-	-	-	1.05	1.04	1.03-1.06	<0.001
Don't know	342	16.9	(12.0)	1.2	1.2	1.0-1.4	0.048
Clustering - none	962	14.1	(10.8)	1.0	1.0	-	-
Clustering – any	150	14.8	(11.6)	1.0	1.1	1.0-1.2	0.178
Pyridostigmine bromide (PB)							
None	371	11.2	(8.7)	1.0	1.0	-	-
Any[†]	726	15.8	(11.7)	1.4	1.4	1.2-1.5	<0.001
1–80 tablets taken	152	14.3	(11.6)	1.3	1.3	1.1-1.5	
81–180 tablets taken	156	16.9	(12.0)	1.5	1.4	1.2-1.6	
>180 tablets taken	148	16.9	(12.5)	1.5	1.4	1.2-1.7	
Dose response in those ≥1[‡]				1.2	1.1	1.1-1.2	<0.001
Don't know	318	16.3	(11.6)	1.4	1.4	1.2-1.6	<0.001
Antimalarials							
None	283	12.9	(10.1)	1.0	1.0	-	-
Yes	586	14.8	(11.6)	1.1	1.1	1.0-1.2	0.183
Don't know	543	15.6	(11.1)	1.2	1.1	1.0-1.2	0.087
Anti-biological warfare tablets							
None	540	11.4	(9.6)	1.0	1.0	-	-
Yes	81	19.4	(13.6)	1.7	1.6	1.4-1.9	<0.001
Don't know	792	16.5	(11.3)	1.5	1.4	1.3-1.5	<0.001
Pesticides / insecticides							
No	1026	13.3	(10.3)	1.0	1.0	-	-

	Total number of general health symptoms						
Gulf War exposure	**N**	**Mean**	**(SD)**	**Ratio of means**	**Adj ratio¶**	**CI**	**P value**
Yes	380	18.5	(12.4)	1.4	1.3	1.2-1.5	<0.001
Repellents							
No	1049	14.2	(11.0)	1.0	1.0	-	-
Yes	362	16.1	(11.4)	1.1	1.2	1.1-1.3	0.001
Chemical weapons area							
No	1252	14.1	(10.7)	1.0	1.0	-	-
Yes	152	19.4	(13.0)	1.4	1.3	1.2-1.5	<0.001
Depleted uranium							
No	1184	14.7	(11.2)	1.0	1.0	-	-
Yes	218	14.2	(10.0)	1.0	1.0	0.9-1.1	0.939
MSE questionnaire score							
0–4	320	8.7	(7.4)	1.0	1.0	-	} <0.001
5–8	414	11.5	(8.5)	1.3	1.3	1.2-1.5	
9–12	316	15.8	(10.1)	1.8	1.8	1.6-2.0	
>12	368	22.6	(12.5)	2.6	2.5	2.3-2.8	
Dose response §	-	-	-	1.07	1.07	1.06-1.07	<0.001

* Dose response per unit increase in number of immunisations in those who had received at least one immunisation
† 170 subjects said they took NAPS but did not know how many
‡ Dose response per categorical increase in number of pyridostigmine bromide tablets taken in those who had taken at least one pyridostigmine bromide tablet
§ Dose-response per unit increase in military services experiences score
¶ Ratio of means are adjusted for service type, rank, age (< 20, 20-24, 25 to 34, ≥35 years), education and marital status by negative binomial regression

A similar pattern was found for the analysis of the SF-12 PCS score analysis with the exposure metrics (Table 9.24). A lower (poorer) score was found to be associated with self-reported exposure of 10 or more immunisations, taking pyridostigmine bromide tablets, anti-biological warfare tablets, pesticides/insecticides, being in a chemical weapons area, and military service experiences (particularly 12 or more). Also there were no associations with other exposures such as deployment completed before or after the air war, 'any' immunisations, clustering of immunisations, or DU. A poorer SF-12 PCS score was associated with an increasing number of immunisations, pyridostigmine bromide tablets and military service experiences in a dose response relationship. There was an additional association found between the SF-12 PCS score and antimalarials, of borderline statistical significance, which had not been found for the symptom score analysis.

Table 9.24 Subanalysis of Gulf War veteran SF-12 PCS score by exposures and experiences

Gulf War exposure*	SF-12 Physical Component Summary score					
	Mean	(SD)	Diff	Adj Diff Ý	95% CI	P value
Deployment completed before air war						
Yes	49.8	(8.5)	0.0	0.0	-	-
No	49.1	(9.4)	-0.7	-0.4	-1.6, 0.7	0.469
Immunisations						
None	50.1	(8.9)	0.0	0.0	-	-
Any	49.7	(8.8)	-0.4	-0.9	-2.7, 0.8	0.302
1-4	51.4	(7.6)	1.3	0.7	-1.3, 2.7	
5-9	49.4	(9.0)	-0.7	-1.2	-3.0, 0.7	
10 or more	47.1	(9.6)	-3.1	-3.9	-6.3, -1.6	
Dose response in those ≥1†	-	-	-0.4	-0.5	-0.7, -0.3	<0.001
Don't know	47.6	(10.4)	-2.6	-2.9	-4.9, -0.9	0.004
Clustering - none	49.8	(8.7)	0.0	0.0	-	-
Clustering – any	48.8	(9.4)	-1.1	-1.4	-2.9, 0.2	0.090
Pyridostigmine bromide						
None	50.8	(8.8)	0.0	0.0	-	-
Any	48.8	(9.2)	-1.9	-2.5	-3.8, -1.2	<0.001
1–80 tablets taken	50.0	(8.0)	-0.7	-1.2	-3.0, 0.6	
81–180 tablets taken	48.5	(10.0)	-2.2	-2.6	-4.4, -0.7	
>180 tablets taken	47.8	(9.5)	-2.9	-3.4	-5.3, -1.5	
Dose response in those ≥1‡			-1.0	-1.2	-1.8, -0.6	<0.001
Don't know§	48.3	(9.3)	-2.5	-2.8	-4.3, -1.4	<0.001
Antimalarials						
None	50.6	(8.5)	0.0	0.0	-	-
Yes	48.9	(9.3)	-1.7	-1.5	-2.8, -0.1	0.035
Don't know	48.7	(9.4)	-1.8	-1.6	-3.0, -0.2	0.026
Anti-biological warfare tablets						
None	50.7	(8.4)	0.0	0.0	-	-
Yes	47.0	(9.8)	-3.7	-3.6	-5.8, -1.5	0.001
Don't know	48.4	(9.6)	-2.5	-2.3	-3.4, -1.3	<0.001
Pesticides / insecticides						
No	50.2	(8.6)	0.0	0.0	-	-
Yes	46.5	(10.2)	-3.7	-3.4	-4.6, -2.3	<0.001

Gulf War exposure*	SF-12 Physical Component Summary score					
	Mean	(SD)	Diff	Adj Diff Ý	95% CI	P value
Repellents						
No	49.5	(9.2)	0.0	0.0	-	-
Yes	48.4	(9.2)	-1.1	-1.1	-2.3, 0.03	0.055
Chemical weapons area						
No	49.6	(8.9)	0.0	0.0	-	-
Yes	46.0	(10.7)	-3.6	-3.7	-5.3, -2.1	<0.001
Depleted uranium						
No	49.3	(9.2)	0.0	0.0	-	-
Yes	49.1	(9.1)	-0.2	-0.2	-1.6, 1.1	0.718
MSE questionnaire score						
0–4	51.9	(6.6)	0.0	0.0	-	
5–8	50.3	(8.3)	-1.6	-1.8	-3.2, -0.5	
9–12	49.4	(9.8)	-2.5	-2.7	-4.1, -1.3	<0.001
>12	45.6	(10.5)	-6.3	-6.5	-7.9, -5.1	
Dose response¶	-	-	-0.5	-0.5	-0.5, -0.4	<0.001

* The numbers for each exposure categories are reported in the Table 9.23
† Dose response per unit increase in number of immunisations in those who had received at least one immunisation
‡ Dose response per categorical increase in number of pyridostigmine bromide tablets taken in those who had taken at least one pyridostigmine bromide tablet
§ 170 subjects said they took NAPS but did not know how many
¶ Dose-response per unit increase in military service experiences score
Ý Difference in means are adjusted for service type, rank, age (< 20, 20-24, 25 to 34, ≥35 years), education and marital status by linear regression

The overall findings for the analysis of the SF-12 MCS score by exposure metrics are shown in Table 9.25 and are very similar to the findings for the general health symptoms and SF-12 PCS score. A lower (poorer) SF-12 MCS score was associated with similar self reported exposures; self-report exposure to pyridostigmine bromide, anti-biological warfare tablets, 10 or more immunisations, pesticides/insecticides, being in a chemical weapons area, and MSE questionnaire score. There were no associations with the same exposures, such as 'any' immunisations, clustering of immunisations, antimalarials or DU. Increasing number of immunisations and increasing number of stressful military service experiences were associated with a poorer SF-12 MCS score in a dose response relationship. Poorer SF-12 MCS scores in those veterans still deployed at the time of the air war, was of borderline statistical significance.

The dose response relationship to increasing level of military service experiences was more marked for the SF-12 MCS score than for the SF-12 PCS score.

Table 9.25 Subanalysis of Gulf War veteran SF-12 MCS score by exposures and experiences

Gulf War exposure*	SF-12 Mental Component Summary score					
	Mean	**(SD)**	**Diff**	**Adj Diff[Ý]**	**CI**	**P value**
Deployment completed before air war						
Yes	48.9	(9.9)	0.0	0.0	-	-
No	47.0	(11.5)	-1.9	-1.4	-2.8, -0.04	0.043
Immunisations						
None	47.0	(12.4)	0.0	0.0	-	-
Any	48.2	(10.8)	1.2	2.0	-0.1, 4.2	0.061
1-4	50.1	(9.9)	3.1	3.7	1.3, 6.1	
5-9	47.9	(10.8)	0.8	1.7	-0.5, 3.9	
10 or more	45.6	(11.9)	-1.4	-0.2	-3.0, 2.6	
Dose response in those ≥1[†]	-	-	-0.5	-0.4	-0.6, -0.2	0.001
Don't know[‡]	45.5	(11.4)	-1.5	-0.2	-2.6, 2.2	0.885
Clustering - none	48.0	(11.0)	0.0	0.0	-	-
Clustering – any	48.0	(11.0)	0.1	-0.4	-2.3, 1.6	0.722
Pyridostigmine bromide						
None	49.5	(10.6)	0.0	0.0	-	-
Any	46.7	(11.4)	-2.7	-2.0	-3.6, -0.4	0.012
1–80 tablets taken	48.6	(10.3)	-0.9	-0.9	-2.5, 1.8	
81–180 tablets taken	44.8	(11.9)	-4.6	-2.9	-5.1, -0.6	
>180 tablets taken	46.7	(11.8)	-2.8	-1.3	-3.6, 1.0	
Dose response in those ≥1[§]			-1.3	-0.7	-1.4, 0.1	0.068
Don't know	46.6	(11.0)	-2.9	-2.4	-4.2, -0.6	0.008
Antimalarials						
None	48.4	(11.3)	0.0	0.0	-	-
Yes	47.5	(11.0)	-0.8	-0.6	-2.2, 1.1	0.502
Don't know	47.0	(11.2)	-1.4	-0.7	-2.4, 1.0	0.406
Anti-biological warfare tablets						
None	49.6	(10.4)	0.0	0.0	-	-
Yes	44.7	(11.6)	-4.9	-4.1	-6.7, -1.5	0.002
Don't know	46.3	(11.4)	-3.2	-2.7	-4.0, -1.4	<0.001
Pesticides / insecticides						
No	48.4	(10.8)	0.0	0.0	-	-

Gulf War exposure*	SF-12 Mental Component Summary score					
	Mean	(SD)	Diff	Adj Diff Ý	CI	P value
Yes	44.8	(11.9)	-3.6	-3.4	-4.8, -2.1	<0.001
Repellents						
No	47.5	(11.2)	0.0	0.0	-	-
Yes	47.3	(11.3)	-0.2	-0.5	-1.9, 0.9	0.476
Chemical weapons area						
No	48.0	(10.9)	0.0	0.0	-	-
Yes	43.3	(12.4)	-4.7	-4.3	-6.2, -2.3	<0.001
Depleted uranium						
No	47.5	(11.3)	0.0	0.0	-	-
Yes	47.4	(10.9)	-0.1	-0.1	-1.1, 1.6	0.947
MSE questionnaire score						
0–4	52.1	(8.4)	0.0	0.0	-	<0.001
5–8	49.8	(10.2)	-2.3	-2.2	-3.7, -0.6	
9–12	46.3	(10.8)	-5.8	-5.5	-7.2, -3.8	
>12	41.5	(12.0)	-10.6	-10.0	-11.6, -8.4	
Dose response¶	-	-	-0.8	-0.7	-0.8, -0.6	<0.001

* The numbers for each exposure categories are reported in the Table 9.23
† Dose response per unit increase in number of immunisations in those who had received at least one immunisation
‡ Dose response per categorical increase in number of pyridostigmine bromide tablets taken in those who had taken at least one pyridostigmine bromide tablet
§ 170 subjects said they took NAPS but did not know how many
¶ Dose-response per unit increase in military service experiences score
Ý Difference in means are adjusted for service type, rank, age (< 20, 20-24, 25 to 34, ≥35 years), education and marital status by linear regression

Functional impairment in Gulf War veterans during the past 2 weeks also had a similar pattern when analysed by exposure metrics. The results are shown in Table 9.26, which shows that functional impairment was associated with 'any' immunisations, antimalarials, anti-biological warfare tablets, pesticides/insecticides, repellents, being in a chemical weapons area, and number of military service experiences. Increasing number of immunisations received, increasing number of pyridostigmine bromide tablets taken and increasing level of stressful military service experiences was associated with functional impairment in a dose response relationship.

Table 9.26 Subanalysis of Gulf War veterans with functional impairment by exposures and experiences

Gulf War exposure*	Gulf War veterans with functional impairment during the past 2 weeks					
	n	%	Crude OR	Adj OR[Ý]	CI	P value
Deployment completed before air war						
Yes	55	17	1.0	1.0	-	-
No	240	22	1.4	1.2	0.9-1.7	0.202
Immunisations						
None	25	21	1.0	1.0	-	-
Any	181	19	0.9	0.8	0.5-1.4	0.446
1–4	29	11	0.5	0.5	0.3-0.8	
5–9	116	21	1.0	0.9	0.5-1.5	
10 or more	36	29	1.5	1.4	0.8-2.7	
Dose-response in those ≥1[†]	-	-	1.1	1.1	1.1-1.2	<0.001
Don't know[‡]	87	25	1.3	1.1	0.7-1.9	0.676
Clustering - none	187	20	1.0	1.0	-	-
Clustering – any	31	21	1.1	1.1	0.7-1.8	0.586
Pyridostigmine bromide						
None	54	15	1.0	1.0	-	-
Any	104	23	1.7	1.8	1.2-2.6	0.004
1–80 tablets taken	21	14	0.9	1.0	0.5-1.8	
81–180 tablets taken	37	24	1.8	1.7	1.0-2.9	
>180 tablets taken	46	31	2.6	2.5	1.5-4.2	
Dose response in those ≥1[§]	-	-	1.4	1.4	1.2-1.6	<0.001
Don't know	79	25	1.9	2.1	1.3-3.1	0.001
Antimalarials						
None	44	16	1.0	1.0	-	-
Yes	129	22	1.5	1.5	1.0-2.3	0.037
Don't know	120	22	1.5	1.5	1.0-2.2	0.059
Anti-biological warfare tablets						
None	74	14	1.0	1.0	-	-
Yes	22	27	2.3	2.1	1.2-3.8	0.010
Don't know	197	25	2.1	2.0	1.5-2.8	<0.001
Pesticides / insecticides						
No	190	19	1.0	1.0	-	-

Gulf War exposure*	Gulf War veterans with functional impairment during the past 2 weeks					
	n	%	Crude OR	Adj OR[Ý]	CI	P value
Yes	100	26	1.6	1.5	1.1-2.0	0.013
Repellents						
No	202	19	-			
Yes	91	25	1.4	1.4	1.0-1.9	0.025
Chemical weapons area						
No	234	19	1.0	1.0	-	-
Yes	55	36	2.5	2.3	1.6-3.4	<0.001
Depleted uranium						
No	245	21	1.0	1.0	-	-
Yes	47	22	1.1	1.1	0.8-1.6	0.617
MSE questionnaire score						
0–4	37	12	1.0	1.0	-	
5–8	61	15	1.2	1.3	0.9-2.1	} <0.001
9–12	63	20	1.9	1.9	1.1-3.0	
>12	134	36	4.3	4.2	2.7-6.3	
Dose response[¶]	-	-	1.1	1.1	1.1-1.1	<0.001

* The numbers for each exposure categories are reported in the Table 9.23
†† Dose response per unit increase in number of immunisations
‡ Dose response per categorical increase in number of pyridostigmine bromide tablets taken
§ 170 subjects said they took NAPS but did not know how many
¶ Dose-response per unit increase in military service experiences score
Ý Odds ratios are adjusted for service type, rank, age (< 20, 20-24, 25 to 34, ≥35 years), education and marital status by logistic regression

9.5 Discussion

This chapter reports the results of a number of different measures of general health including the self-reported symptoms, doctor diagnosed or treated medical conditions, physical and mental health status as measured by the SF-12, as well as objective physical examination measures such as BMI, WHR, waist circumference, blood pressure and a fitness test. Further analyses of self-reported symptoms (by severity) and medical conditions (by doctor assessment of the likelihood of the diagnosis) were used to increase the accuracy of the self-reported information.

One of the main findings of these analyses is that Gulf War veterans report significantly more health symptoms than the comparison group. In addition, Gulf War veterans are more likely to report symptoms that are more severe in nature. Gulf War veterans also report some, but not all, medical conditions that were first diagnosed in 1991 or since more commonly than the comparison group. The conditions with the largest associations with Gulf War service include posttraumatic stress disorder, skin conditions and gastrointestinal conditions. While back, neck and other joint problems were the most commonly reported medical conditions in the Gulf War veterans, these were also the most commonly reported conditions in the comparison group, with little difference between the two groups.

The differences between the Gulf War veteran group and comparison group are more marked for the self-reported symptoms than for the self-reported medical conditions. Gulf War veterans are about as likely to report medical conditions that were subsequently assessed as a possible or probable diagnosis, as the comparison group. A similar and high proportion (over 90%) of medical conditions reported by both study groups were assessed as being a possible or probable diagnosis, indicating a similar and small amount of over-reporting in either group.

The most commonly reported symptoms in both study groups are neuropsychological symptoms. There was a trend, that was of borderline statistical significance, for the differences between the Gulf War group and comparison group to be greater in the younger age group and in those of 'other ranks – non supervisory' rank. In both study groups, a relatively greater proportion of the Army participants reported individual symptoms compared with their Navy and Air Force counterparts.

There are some differences between the Gulf War veteran and comparison groups of the ordering by frequency of symptoms and medical conditions, but the overall patterns symptom reporting and medical conditions reporting is similar between the study groups and when they are broken down by service type. Those symptoms and medical conditions which are most commonly reported by the Gulf War group also tend to be most commonly reported by the comparison group, although the frequency of reporting is higher in the Gulf War veteran group.

Gulf War veterans have slightly poorer physical health status, but a more markedly poorer mental health status, as measured by the SF-12, than the comparison group. A significantly greater proportion of Gulf War veterans have PCS-12 and MCS-12 scores that are lower than the 25^{th} percentile for the US population norms than the comparison group. Furthermore, a greater proportion of Gulf War veterans report functional impairment over the past two weeks. Although Gulf War veterans report more symptoms and medical conditions overall, this is not reflected in a greater rate of recent health care utilisation, as measured through hospitalisations or current use of medication.

When physical measures of general health are considered, the Gulf War veterans and comparison group are very similar. The exception is waist-to-hip ratio (WHR) for which significantly fewer Gulf War veterans have a WHR >0.9 indicating less risk of later obesity related complications. There are no significant differences between the groups with respect to blood pressure and body mass index. Gulf War veterans did, however, tend to have a slightly lower level of fitness as measured by the step test, but this, again, did not reach statistical significance.

The total number of symptoms reported, the physical and mental health summary scores of the SF-12 and functional impairment were associated in a similar pattern with several self-reported exposures that occurred in the Gulf War. These included 10 or more immunisations, stressful military services experiences, pyridostigmine bromide tablets, anti-biological warfare tablets, pesticides/insecticides and report of being in a chemical weapons area. General health symptoms, but not the SF-12 measures, were also associated with reported exposure to repellents. Further, the SF-12 physical health measure was associated with reported exposure to antimalarials and the mental health measure was associated with deployment completed before or after the air war. None of these health outcomes were associated with reported exposure to depleted uranium or to clusters of immunisations received within a one-week period.

These general health outcomes were also worse in those who reported that they did not know whether they had received medication such as pyridostigmine bromide, antimalarials or anti-biological warfare tablets or the number of immunisations they received. The interpretation of this is not clear. It is possible, given the feedback from participants followed up during the data checking process, that these individuals may have received such medications or immunisations but were hesitant to commit to a response when they were not sure and where documentation of this was not available.

Several of the findings of this study are similar to those of other epidemiological studies of Gulf War veterans. Most of these studies have found an increased reporting of multiple symptoms by Gulf War veterans{Unwin, 1999 #199;Iowa Persian Gulf Study Group, 1997 #197;Cherry, 2001 #295;Fukuda, 1998 #75;Haley, 1997 #88;Kang, 2000 #787;Goss Gilroy Inc., 1998 #651;Ishoy, 1999 #112;Wolfe, 1998 #214] and a similar order of symptoms reported by the Gulf War group and their comparison group within the study population.[21, 157] In addition, the symptoms most commonly reported by Gulf War veterans in our study are similar to those reported by US and UK Gulf War veterans. The difference between Gulf War veterans and comparison group on the reporting of symptoms in our study do, however, appear to be less marked than between study groups in some other studies where the odds ratios tend to be greater.[20, 21, 157, 160] One of the difficulties with making direct comparisons between studies can be the use of different terminology and definitions for symptoms in the different studies. The symptom questionnaire in our study was based on that used by Unwin *et al*.[21] A comparison of their published data (rounded to the nearest integer), with the data of our study, shows that while our Gulf War veteran group reports slightly higher prevalences than the UK Gulf War veteran group, our comparison group had considerably higher prevalences than the UK era (comparison) group (Table 9.27).

Table 9.27 Comparison of the prevalences and odds ratios of the 10 symptoms most commonly reported by Australian Gulf War veterans with those reported by UK Gulf War veterans

Symptom	GWV %	Comp grp %	Adj OR	UK GWV* %	UK Era grp %	Adj OR
Feeling unrefreshed after sleep	66	56	1.6	56	32	2.7
Fatigue	66	56	1.6	50	28	2.7
Headaches	61	54	1.3	54	36	2.1
Sleeping difficulties	60	49	1.6	48	28	2.4
Irritability / outbursts of anger	57	46	1.6	55	26	3.7
Low back pain	52	49	1.6	-	-	-
General muscle aches or pains	52	46	1.3	-	-	-
Flatulence or burping	46	40	1.3	34	-	-
Forgetfulness	46	34	1.7	45	17	4.2
Difficulty finding the right word	45	35	1.6	-	-	-

*Reproduced from Unwin *et al*, 1999 Health of UK servicemen who served in the Gulf War[21]

In several other studies, the pattern of self-reporting of medical conditions has been similar to that of symptoms, although not as consistent or evident, with Gulf War veterans reporting many,[16, 20] or all,[21] of the medical conditions more frequently than non-Gulf veterans. It is

difficult to make comparisons between studies on the medical conditions most commonly reported by study populations or groups because of the differences in medical terminology or the definitions used,[20, 21] but there appears to be less similarity in the ordering of medical conditions in our study compared with that of Unwin *et al*,[21] than was found for the ordering of symptoms.

The differences between functional impairment and hospitalisations in Gulf War veterans and the comparison group reported in our study were not as marked as those reported by Kang *et al*[20] where US Gulf War veterans were twice as likely as non-Gulf veterans to report staying home all or part of a day because they did not feel well as a result of illnesses or injury, and a significantly greater proportion of Gulf War veterans reported hospitalisations in the last year.

Gulf War veterans have been found to have significantly lower health status and quality of life in previous studies. UK Gulf War veterans had significantly poorer health perception but not significantly poorer physical functioning, measured by the SF-36 (of which the SF-12 Health Survey is a subset), than Bosnia and Era veterans.[21] The Iowa group found diminished physical functioning across all subscales of the SF-36, with large absolute differences between the groups for bodily pain, general health and vitality.[16, 353]

Compared with Australian normative data, Australian Gulf War veterans scored more poorly on the self-reported SF-12 physical and mental functioning scales. The Australian National Survey of Mental Health and Wellbeing of Adults (NSMHWB)[260] found a mean PCS-12 score of 52.34 and a mean MCS-12 score of 54.25 for adults with no mental disorders or physical conditions. In adults with physical conditions only, a mean PCS-12 of 44.47 and a mean MCS-12 of 53.75 were found in the NSMHWB. In adults with mental conditions only, a mean PCS-12 of 51.39 and a mean MCS-12 of 46.83 were found in that study.[260] Therefore, Australian Gulf War veterans have lower PCS-12 and MCS-12 scores than the general Australian population.

Poor self perception of health and self-ratings of health have been shown to be important predictors of future health care use and of mortality.[292, 354, 355] Leading indicators such as increased stress, poorer perception of health and premorbid indicators of ill-health may lead to more obvious health problems or increased mortality in the future. This suggests that male Gulf War veterans are at higher risk of health problems in the future than the comparison group and males in the Australian population.

Normative Australian data are available on obesity and it has been estimated that 60% of Australians aged 25 years and over are overweight or obese (BMI $\geq$25) and that 21% of the population aged 21 years and over are obese (BMI $\geq$30). The proportions of both our study groups considered to be overweight or obese were greater than these general population figures.[292] In 1999-2002, 55% of Australian men had a waist circumference greater than 94cm and almost 27% of men had a waist circumference greater than 102cm. Compared with these population figures, greater proportions of both of our study groups than the general Australian population had waist circumferences greater than 94cm and greater than 102cm.[292] As these measures are predictive of future health status, our findings suggest that Gulf War veterans and the comparison group subjects are at increased risk of future health problems than the Australian male population.

Some of the findings of our study are similar to those of other studies with respect to the effect of service type, age and rank. Symptom severity scores have been found to be greater in UK Gulf War veterans, and in younger people (<25 years), ranks other than officers and in

those who served in the Army.[157] Higher prevalence rates of symptoms and higher rate differences have been reported for Army Gulf War veterans and in comparison with Army non-Gulf veterans respectively.[20] Our finding of rank being associated with ill-health (as measured by mean total symptom score) has also been reported by Ismail *et al*,[155] but we found the effect of rank is similar for both the Gulf War and comparison groups.

The associations of general health outcome measures with some self-reported exposures have been examined in several studies, and some exposures which we found to be associated with a number of different health outcome measures have also been found in some of these studies. Increased reporting of, or severity of, symptoms has been associated with several different Gulf War exposures. Cherry *et al*[28] found that the number of vaccinations, days handling pesticides and days exposed to smoke from oil well fires, reported days of use of NAPS tablets and insect repellent, feelings that life was in danger, need for medical attention while in the Gulf, and side effects from NAPS tablets were all associated with a higher symptom severity score.

The Iowa Persian Gulf Study group[16] also found that, among Gulf War veterans, most of the self-reported exposures were significantly related to many of the medical and psychiatric conditions. Unwin *et al*[21] found that multiple chemical, environmental and military service experiences exposures showed associations with SF-36 physical functioning and CDC syndrome, as well as the other health outcome measures of self-reported health perception, fatigue case criteria, post-traumatic stress reaction and the GHQ-12 case criteria in the Gulf War, Bosnia and Era cohorts. Belief of being in a chemical weapons area was associated with low health, CDC multi-symptom illness, the GHQ case criteria and fatigue case criteria.[21] Biological warfare vaccinations and multiple routine vaccinations were associated with the CDC multisymptom syndrome in Gulf War veterans,[21] and receipt of multiple immunisations during deployment was associated with increased risk of adverse health outcomes.[61] While we found that having at least 10 vaccinations seemed to increase the risk of adverse general health outcomes, we did not find that clustering of immunisations was associated with any of our general health outcomes.

When considering the impact on health of these Gulf War exposures and experiences, it is important to remember that many relied on self-report, where little, if any, objective documentation was available for them. While some of the stronger findings in relation to the link between general health measures and exposures, such as being in an area where chemical weapons were believed to have been used or taking pyridostigmine bromide, were only based on self-report, there were several other exposures where other information was used. One example is for immunisations, where veterans were able to refer to their immunisation book, although it needs to be acknowledged that the quality of the information in these books was very variable. Another exposure factor for which we found positive associations with general health outcomes was pesticide use. This was partly based on self-report, but the classification also took into account knowledge of those jobs during the Gulf War for which pesticide use was part of the duties.

One aspect of the study, which limited our ability to investigate some potential associations within the analysis, was the relatively small numbers of Army and Air Force participants. This meant that there was limited statistical power to fully explore possible differences in general health outcomes between the study groups for these service types.

There were also some limitations in data quality for some variables. These are discussed in detail in the chapter 'Reported Gulf War and other exposures'. One example is the data available on immunisations. Eight percent of veterans reported receiving no immunisations

and 24% reported that they did not know how many immunisations they had received. Veterans who had their immunisation books reported higher numbers of immunisations than subjects who did not have their immunisation books. They were also less likely to report that they had not received any immunisations. For almost all listed individual immunisations, more than 30% of the veterans did not know whether they had received them or not. For an immunisation such as anthrax, 15% reported immunisation against anthrax but 58% were unsure. The uncertainty of the Gulf War veterans regarding the number and types of immunisations that they received has limited our ability to assess the associations between immunisations and the health outcomes under study, both in this chapter and in other chapters of this report. This data quality problem tends to weaken the strength of our conclusions regarding the impact of immunisations during the Gulf War and their possible impact on health. This has important implications for the Australian Defence Force for improving future record keeping in relation to immunisations and other aspects of deployment.

The general evaluation of participation bias in this study (see chapter 6) has indicated that effects on odds ratios are likely to be small and therefore participation bias is unlikely to explain the differences (or lack of differences) that we found in health status between the Gulf War veterans and the comparison group. More directly, the non-participation imputation procedure detailed in the Recruitment chapter was applied to three general health outcomes to examine differences between the Gulf War Veterans and comparison group subjects. These were the prevalence of self-reported fatigue in the last month, doctor-diagnosed back or neck problems since 1991, and post-traumatic stress disorder (PTSD) diagnosed since 1991. These outcomes represent high prevalence, a null odds ratio, and an elevated odds ratio, respectively. The results of this analysis revealed only minor effects of non-participation. The mean of the age, rank and service-adjusted odds ratios from the imputation procedure correcting for non-participation for self-reported fatigue was 1.36, which is only marginally lower than the corresponding odds ratio of 1.42 among participants. For back/neck problems and PTSD, the corresponding results were 0.97 (imputed) versus 0.99 (participants), and 2.85 (imputed) versus 2.86 (participants), respectively. Some caution should be applied to the interpretation of these analyses, as they are based on statistical models with underlying assumptions and also assume that the SF-12 data from the telephone-questionnaire participants is representative of the corresponding (unobserved) data for the non-participants (see chapter 6 for more detail).

Information bias may have affected the results of this study, if Gulf War veterans were more susceptible to external influences, from avenues such as the media, on self-reporting of symptoms or medical complaints. This source of bias would not have affected the objective measures of physical health which were used to assess the health status of both groups, and we found some differences between groups on some of these measures, eg the WHR. Analyses were undertaken to increase the accuracy of the self-reporting of medical conditions by participants, and thereby limit information bias, by using the HSA doctors to assess the likelihood of self-reported medical conditions. This resulted in little change in the observed health differences between the two groups, suggesting that information bias was not a major factor in the reporting of medical conditions. Also, there was little difference between the Gulf War and comparison groups in the rates of reported diagnoses that were later assessed as non-medical or unlikely, indicating that over-reporting by the Gulf War veteran group in relation to medical diagnoses was not a significant factor in our study.

There was a slightly higher reporting by the comparison group of many medical conditions that were first diagnosed in 1990 or earlier. There may be a number of interpretations for this finding. One interpretation is that our comparison group participants are at the less healthy

end of the health/disease spectrum, ie of the comparison group people approached, those who had health problems tended to participate and those without such problems did not participate. This could also apply to the Gulf War veterans too, albeit with a smaller percentage of non-participation. This could mean that we are overestimating health problems in the comparison group, and that the odds ratios for the various general health measures are possibly underestimates. Another possible interpretation is that this is a form of information bias. We have asked for a 10 year recall of conditions, and this could be different for the Gulf War and comparison group subjects, as the Gulf War group has a well defined reference point, whereas the comparison group does not. Gulf War veterans may be more likely to date the development of any disorders post Gulf War as this event is a very prominent one for them. This may mean that the onset of medical conditions in some comparison group subjects may be misclassified as pre Gulf War when really they were post Gulf War, whereas for the Gulf War veterans the opposite may be more likely.

In the analysis, we controlled for a core set of the usual confounders known to impact on health status, but it is possible that other confounders not identified may have impacted on the results. However, this is unlikely to explain the differences found.

Many of the conclusions of other epidemiological studies of Gulf War veterans' health have been based solely on self-reported findings. The use of physical measures of general health has increased the objectivity of our study, but there is limited physical health data from other veteran cross-sectional studies with which to compare our results. The instruments for self-reporting symptoms and medical conditions used in our study have most similarities with those of Unwin *et al*,[21] but comparisons at this stage are limited to published data. A more detailed comparative analysis of the results of our study and those of another study such as that of Unwin *et al*, who used a comparable instrument in the postal questionnaire, would be of value.

There are a number of aspects of the general health findings, which are not directly relevant to the central research questions of this study, but which we think should be evaluated further in relation to military service in general. For example, further evaluation of the factors causing a higher than expected BMI in both groups would be useful. This finding may have important health implications for military service in general, as this can increase the risk of ill-health in the future. Back, neck and joint disorders were the medical conditions which were reported most commonly in both groups. The reasons for this are not clear, but this is important to explore further in order to identify those service activities where prevention measures could be introduced to reduce the incidence of such joint disorders.

9.5.1 Summary of findings

In summary, and in relation to the research questions, Gulf War veterans have more self-reported health symptoms than the comparison group. The more common symptoms relate to neuropsychological and musculoskeletal systems. In addition, the severity of these symptoms reported by Gulf War veterans is greater than the comparison group. Younger veterans and those of lower rank tended to report more symptoms

Gulf War veterans report some but not all medical conditions that were first diagnosed in 1991 or since more commonly than the comparison group. The most commonly reported medical conditions were of the musculoskeletal system, skin and psychological conditions. There was no evidence of over-reporting of medical conditions by the Gulf War veterans. A similar, and high, proportion (over 90%) of medical conditions reported by both study groups were assessed as having a high likelihood of diagnosis. Gulf War veterans seemed to be

slightly healthier than the comparison group prior to the Gulf War, based on fewer self-reported diagnoses before 1991.

Gulf War veterans have more self-reported functional impairment due to illness or injury over the past two weeks than the comparison group, but do not have more self-reported hospitalisations or more current use of medication than the comparison group

Gulf War veterans have slightly poorer physical health status, but a markedly poorer mental health status, as measured by the SF-12, than the comparison group. A significantly greater proportion of Gulf War veterans have PCS-12 and MCS-12 scores that are lower than the 25th percentile for the US population norms than the comparison group.

Gulf War veterans have similar physical health status to the comparison group, as assessed by objective measurements, such as body mass index, waist circumference, waist hip ratio, blood pressure and fitness as measured by a step test.

Several Gulf War related exposures and experiences are associated with some of these adverse general health outcomes. The total number of self-reported symptoms in the past month was associated with several exposures, including having more than 10 immunisations, pyridostigmine bromide, anti-biological warfare tablets, pesticides/insecticides, repellents, being in a chemical weapons area, and military service experiences, but not with some other exposures such as clustering of immunisations, or reported exposure to depleted uranium.

A lower (poorer) SF-12 physical score and a poorer SF-12 mental score were both associated with several Gulf War exposures, including pyridostigmine bromide tablets, anti-biological warfare tablets, pesticides/insecticides, being in a chemical weapons area, and military service experiences. The physical score was also associated with taking antimalarials.

Functional impairment during the past 2 weeks was associated with having immunisations, antimalarials, anti-biological warfare tablets, pesticides/insecticides, repellents, being in a chemical weapons area, and level of military service experiences.

Serving in the Gulf during or after the commencement of the air war did not appear to increase the risk of developing these adverse general health outcomes, suggesting that the important factors in increasing the risk of these adverse health outcomes were not related to the air and ground war themselves.

10. Laboratory investigations

Participants who undertook medical assessments provided several blood samples for haematological, biochemistry and serological analysis, and this chapter reports the results of these laboratory investigations.

One laboratory was used in this study to minimise sources of variation, and to standardise the testing methodology and reference intervals for blood specimens that were collected from participants across Australia. The reason for this is that equipment, testing methodologies and reference intervals can vary between laboratories and in different states and territories. The laboratory used was the Institute of Medical and Veterinary Science (IMVS) in Adelaide, South Australia. The laboratory investigations, the reference intervals and the testing methodologies used by IMVS are detailed in appendix 6. Early in the study, the laboratory investigations for 18 study participants were performed by Dorevitch Pathology (also a NATA and RCPA Registered Laboratory) in Melbourne, and the test results have been included in the analysis, where appropriate, utilising that laboratory's own reference intervals.

10.1 Aim

The aim of this analysis is to investigate whether male Australian Defence Force personnel who served in the Gulf War have a higher prevalence of laboratory test results that are indicative of adverse health effects than the comparison group; and, if so, whether these effects are associated with exposures and experiences that occurred in the Gulf War?

10.2 Research questions

1. Do Australian Gulf War veterans have significantly more haematological test results that are indicative of anaemia or inflammation than the comparison group?
2. Do Australian Gulf War veterans have significantly more biochemical test results that are indicative of renal impairment or liver disease or of raised blood glucose than the comparison group?
3. Do Australian Gulf War veterans have serological test results that are indicative of significantly more exposure to viral infections than the comparison group?
4. Do Australian Gulf War veterans have more abnormalities on urinalysis testing than the comparison group?

10.3 Definitions

10.3.1.1 Overview of parameters for analysis

The parameters used to compare the study groups in the analysis were decided prior to the data analysis commencing, and included those parameters considered to have either a scientific rationale through biological plausibility or where results of previous clinical or epidemiological studies indicated their importance. The numbers and proportions of results that were within the reference intervals are routinely reported in the tables for each test. For parameters, such as haemoglobin, where values either higher or lower than the reference intervals may be clinically important, both relationships to the reference interval are reported. Where the clinical importance of a test result related primarily to an elevated value, eg bilirubin, only that relationship to the reference interval is reported. Erythrocyte

Sedimentation Rate (ESR) and C-reactive protein (CRP) have a detection limit, and only results that were within or higher than the reference interval could be reported.

10.3.1.2 Laboratory reference intervals

The primary analysis compared the results of the Gulf War veteran group with those of the comparison group. As a framework for this comparison, the reference intervals of IMVS were used to categorise the test results. In their determination of reference intervals, the distributions of parameters were not assumed to be Normal; and IMVS reported 95th percentile reference intervals with a 2.5% cut-off at both ends; ie 2.5% of the population would be expected to have a value higher, and 2.5% lower, than this interval. These reference intervals were based on the testing of 230 "laboratory normal" staff.

Reference intervals have some limitations for interpreting the clinical significance or meaning of results. If a test result was outside the reference interval it did not necessarily mean that it was abnormal. For example, haemoglobin of 130 g/L was lower than the reference interval of 135-175 g/L for an adult male. This would not usually be considered "abnormal" or of clinical importance, as the person would not be expected to have symptoms of anaemia, such as tiredness, until the haemoglobin was less than 100 g/L. However, test results just above or below a reference value may suggest pre-clinical conditions. Although reference intervals have limitations, they are an established way of presenting and comparing test results between groups. In this study, this limitation in reference intervals is overcome by having a comparison group which is also compared against the same set of reference values.

10.3.1.3 Definitions of laboratory investigation outcomes

Laboratory investigation outcome definitions were developed for the purposes of this study to assist in comparing the health outcomes of the Gulf War veterans and comparison group. The following definitions were based on the IMVS laboratory reference intervals:

- haematology test results indicative of anaemia were defined as Hb <135 g/L.
- haematology test results indicative of inflammation were defined as an Erythrocyte Sedimentation Rate (ESR) >10mm (or >15mm for participants age >50 years) or a C-reactive Protein (CRP) >10 mg/L or a White Cell Count (WCC) >11.0 x 10^9/L.
- biochemical tests results indicative of renal impairment were defined as a creatinine >0.12 mmol/L.
- biochemical tests results indicative of an elevated random plasma glucose were defined as a random plasma glucose >11.0 mmol/L.
- liver function test results indicative of liver disease were defined as:
  - ALP >110 U/L and GGT >60 U/L, which was indicative of obstructive (cholestatic) liver disease
  - ALT >55 U/L and AST >45 U/L, which was indicative of inflammatory (hepatitic) liver disease
- serological test results indicative of prior exposure to viral infections were defined as a:
  - positive EBV antibody test result which was indicative of prior exposure to EBV
  - positive CMV antibody test result which was indicative of prior exposure to CMV
  - positive hepatitis C core antibody test result which was indicative of prior exposure to hepatitis C.

10.4 Results

Of the 2825 participants who completed the medical assessment, 2810 had blood taken. Of these, 1409 (50.1%) were Gulf War veterans and 1401 (49.9%) were comparison group subjects, and 2748 (97.8%) were males and 62 (2.2%) were females. Fifteen (0.5%) did not have blood taken, either because they did not consent or for logistical reasons. This total number of 2810 males includes the 18 participants for whom the Dorevitch Pathology reference intervals have been used. The Dorevitch data was excluded from the calculation of summary statistics such as means (or medians) and standard deviations for individual parameters. The different testing methodologies used by IMVS and Dorevitch Pathology meant that data for these statistics were not directly comparable.

Therefore, in this analysis, the comparisons for males in relation to reference intervals are based on 1379 male Gulf War veterans and 1369 male comparison group participants, and the comparisons on mean (or median) and standard deviation are based on 1365 male Gulf War veterans and 1365 male comparison group participants.

10.4.1 Quality control

The proportion of laboratory investigations for which there was one or more missing value was one of the quality control measures used to monitor progress in the study (Table 10.1).

Table 10.1 Missing values for laboratory investigations

	≥ 1 missing value (N=2810)	
	n	**(%)**
Haematological tests		
Complete Blood Examination (CBE)*	45	(1.6)
Erythrocyte Sedimentation Rate (ESR)	67	(2.4)
Biochemical Analyses		
Urea and Electrolytes (U&Es) †	6	(0.2)
Random plasma glucose	16	(0.6)
Liver Function Tests (LFTs) ‡	2	(0.1)
C-reactive protein (CRP)	1	(0.0)
Serology tests		
Epstein-Barr virus antibody test (EBV IgG)	4	(0.1)
Cytomegalovirus antibody test (CMV IgG)	4	(0.1)
Hepatitis C antibody test (Hep C Ab)	3	(0.1)

* CBE includes haemoglobin, red cell count, packed cell volume, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, white cell count, differential white cell count (neutrophils, lymphocytes, monocytes, eosinophils, basophils) and platelets.
† U&Es include sodium, potassium, chloride, bicarbonate, anion gap, urea, creatinine, ionised calcium and phosphate.
‡ LFTs include total bilirubin, total protein, albumin, globulin, gamma-glutamyl-transferase (GGT), alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and lactate dehydrogenase.

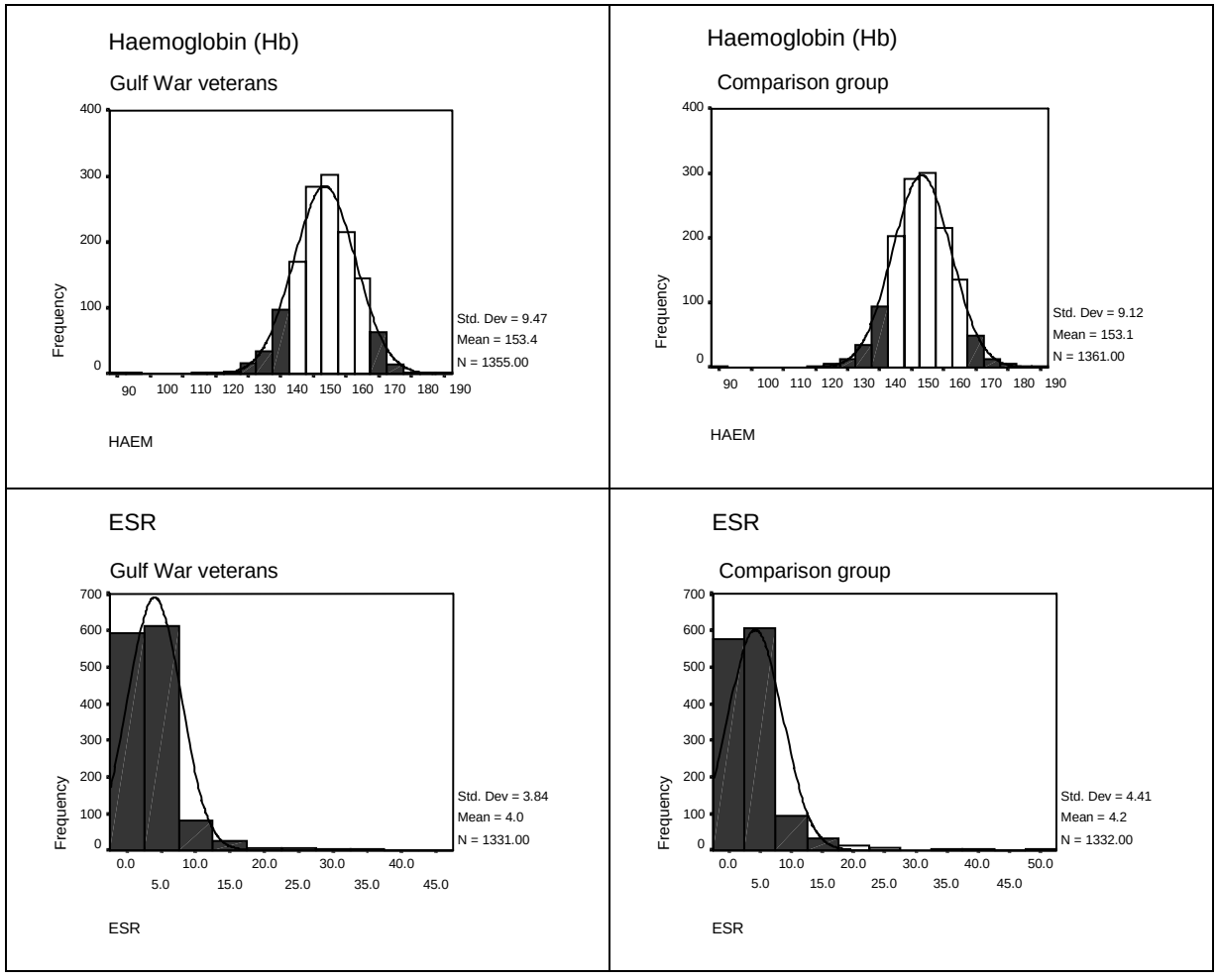
These quality control results were very good, with very low proportions of missing values for all tests, especially when it is considered that this was a national study with the bloods transported across Australia to the one laboratory. The proportions of missing values for some tests such as CBE or ESR were slightly higher than others, and this was attributed to the

inherent sensitivity of these tests to handling procedures, and the time between blood collection and analysis. There was no difference in the rates of missing values for the Gulf War group and comparison group (data not tabulated).

10.4.2 Gulf War vs non-Gulf War comparisons

We reviewed the distribution curves for all parameters. The distribution curves were within expectations, with an essentially normal (bell-shaped) distribution for the central portion of the curve, with a right hand skew at the higher end of values. Distributions for those parameters such as ESR and CRP, which have a detection limit, were censored at the lower end. There were no peaks outside the reference intervals at either the higher or lower ends of values. There were no differences in the shapes of the distribution curves for Gulf War veterans and the comparison group. The distributions of two parameters, haemoglobin and ESR, are presented in Figure 10.1 to illustrate these general features.

Figure 10.1 Haemoglobin and ESR distribution curves for Gulf War veterans and comparison group



10.4.2.1 Haematological test results

The haematology results in Table 10.2 show that the mean (and median ESR, eosinophils and basophils) values for the individual parameters for the two groups were very similar.

Table 10.2 Mean and standard deviation (SD) or median (range) for haematological test results

Parameter	GWV (N=1355) mean (SD)	Comp grp (N=1361) mean (SD)	P value*
Haemoglobin (Hb), g/L	153.4 (9.5)	153.1 (9.1)	0.181
Mean corpuscular volume (MCV), fl	91.6 (4.7)	91.5 (4.5)	0.474
Mean corpuscular haemoglobin (MCH), pg	30.4 (1.4)	30.5 (1.3)	0.024
White cell count (WCC), x 10^9/L	6.3 (1.7)	6.2 (1.7)	0.568
Neutrophil count, x 10^9/L	3.8 (1.3)	3.7 (1.4)	0.339
Lymphocyte count, x 10^9/L	1.9 (0.5)	1.9 (0.6)	0.970
Monocytes, x 10^9/L	0.4 (0.1)	0.4 (0.1)	0.095
Platelets, x 10^9/L	227.8 (44.4)	231.3 (48.5)	0.203
	Median (range)	**median (range)**	
Eosinophils, x 10^9/L	0.11 (0-1.47)	0.13 (0-1.7)	<0.001
Basophils, x 10^9/L	0.03 (0-0.15)	0.02 (0-0.20)	0.003
Erythrocyte sedimentation rate (ESR), mm/hour	3 (1-106)	3 (1-52)	0.252

* P values obtained using Mann-Whitney / Wilcoxon rank sum tests

There was a higher proportion of Gulf War veterans than comparison group subjects with at least one CBE parameter outside the reference interval (Table 10.3). There was less than one percent of participants in each group with more than 4 parameters outside the reference interval. The mean total number (SD) of haematological test results outside the reference interval was similar in both study groups {Gulf War veteran 0.65 (1.05) vs comparison group 0.58 (1.02); crude ratio of means 1.10, adjusted ratio of means 1.10 95% CI 0.97-1.25, p value 0.130}.

The two groups fell within, or higher or lower than, the reference intervals in similar proportions for the individual haematological parameters (Table 10.3). More than 5% of the ESR results of both groups were greater than the reference interval, but the elevations were marginal in both groups with 98.3% of Gulf War veterans and 97.0% of comparison subjects falling within 5mm/hr of the reference interval. Such marginal elevations are not thought to be of clinical importance. A small proportion of MCV results were higher than the reference intervals and this was equally likely for the two study groups.

Table 10.3 Prevalences and odds ratios (OR) for haematological test results in relation to reference intervals

Parameter	GWV (N=1354)		Comp grp (N=1349)		Crude OR	Adj OR	95% CI	P value
	n	(%)	n	(%)				
Complete Blood Examination								
All within reference (ref) intervals	851	(62.9)	902	(66.9)	-	-	-	-
1-2 outside ref interval	403	(29.8)	355	(26.3)	1.2	-	-	-
3-4 outside ref interval	92	(6.8)	65	(5.9)	1.2	-	-	-
≥ 5 outside ref interval	8	(0.6)	12	(0.9)	0.7	-	-	-
Haemoglobin (Hb)								
within ref interval (135-175 g/L)	1332	(97.4)	1325	(97.1)	-	-	-	-
<135 g/L	29	(2.1)	29	(2.1)	1.0	1.0	0.6-1.7	0.966
>175 g/L	7	(0.5)	11	(0.8)	0.6	0.6	0.3-1.7	0.372
Mean corpuscular volume (MCV)								
within ref interval (80.0-98.0 fl)	1243	(90.9)	1251	(91.6)	-	-	-	-
<80.0 fl	6	(0.4)	3	(0.2)	2.0	2.6	0.6-10.9	0.188
>98.0 fl	119	(8.7)	111	(8.1)	1.1	1.1	0.8-1.4	0.585
Mean corpuscular haemoglobin (MCH)								
within ref interval (27.0-33.0 pg)	1320	(96.5)	1317	(96.5)	-	-	-	-
<27.0 pg	18	(1.3)	8	(0.6)	2.2	2.2	0.9-5.1	0.075
>33.0 pg	30	(2.2)	40	(2.9)	0.8	0.7	0.4-1.2	0.203
White cell count (WCC)								
within ref interval (4.0-11.0 x 10^9/L)	1289	(94.2)	1283	(94.0)	-	-	-	-
<4.0 x 10^9/L	58	(4.2)	56	(4.1)	1.0	1.1	0.7-1.6	0.694
>11.0 x 10^9/L	21	(1.5)	26	(1.9)	0.8	0.7	0.4-1.3	0.334
Neutrophil count								
within ref interval (1.8-7.5 x 10^9/L)	1311	(96.0)	1318	(96.7)	-	-	-	-
<1.8 x 10^9/L	24	(1.8)	16	(1.2)	1.5	1.7	0.9-3.2	0.128
>7.5 x 10^9/L	31	(2.3)	29	(2.1)	1.1	1.0	0.6-1.6	0.844
Lymphocyte count								
within ref interval (1.0-3.5 x 10^9/L)	1331	(97.4)	1325	(97.2)	-	-	-	-
<1.0 x 10^9/L	19	(1.4)	18	(1.3)	1.1	1.4	0.7-2.7	0.375
>3.5 x 10^9/L	16	(1.2)	20	(1.5)	0.8	0.8	0.4-1.6	0.559
Eosinophils								
within ref interval (0.02-0.5 x 10^9/L)	1308	(95.8)	1313	(96.3)	-	-	-	-

Parameter	GWV (N=1354)		Comp grp (N=1349)		Crude OR	Adj OR	95% CI	P value
	n	(%)	n	(%)				
<0.02 x 10^9/L	32	(2.3)	22	(1.6)	1.5	1.3	0.8-2.3	0.302
>0.5 x 10^9/L	26	(1.9)	28	(2.1)	0.9	0.9	0.5-1.6	0.721
Basophils								
within ref interval (0.0-0.1 x 10^9/L)	135	(99.5)	1355	(99.4)	-	-	-	-
>0.1 x 10^9/L	7	(0.5)	8	(0.6)	0.9	0.9	0.3-2.4	0.796
Monocytes								
within ref interval (0.2-0.8 x 10^9/L)	1315	(96.3)	1309	(96.0)	-	-	-	-
<0.2 x 10^9/L	30	(2.2)	26	(1.9)	1.2	1.2	0.7-2.1	0.503
>0.8 x 10^9/L	21	(1.5)	28	(2.1)	0.8	0.8	0.4-1.4	0.354
Platelets								
within ref interval (150-400 x 10^9/L)	1321	(97.4)	1318	(97.6)	-	-	-	-
<150 x 10^9/L	33	(2.4)	23	(1.7)	1.4	1.4	0.8-2.5	0.192
>400 x 10^9/L	2	(0.1)	10	(0.7)	0.2	0.2	0.04-1.0	0.044
Erythrocyte sedimentation rate (ESR) *								
within ref interval*	1264	(94.8)	1257	(94.2)	-	-	-	-
>ref interval*	70	(5.2)	77	(5.8)	0.9	0.9	0.6-1.2	0.496

* ESR reference intervals are 0-10mm (age ≥50 years) and 0-15mm (age ≥50 years)

10.4.2.2 Biochemical test results

Table 10.4 shows that the mean (and median CRP and random blood glucose) values for the individual parameters were very similar for the two groups.

Table 10.4 Mean (SD) or median (range) of biochemical test results

Analyte	GWV N=1365 mean (SD)	Comp grp N=1365 mean (SD)	P value*
Sodium, mmol/L	141.8 (2.0)	141.4 (2.1)	<0.001
Potassium, mmol/L	4.2 (0.3)	4.2 (0.4)	0.081
Urea, mmol/L	5.4 (1.2)	5.5 (1.1)	0.050
Creatinine, mmol/L	0.1 (0.0)	0.1 (0.0)	0.337
Ionised calcium, mmol/L	1.1 (0.0)	1.1 (0.1)	0.446
Phosphate, mmol/L	1.1 (0.2)	1.1 (0.2)	0.187
	median (range)	**median (range)**	
Random plasma glucose, mmol/L	4.7 (1.9-22.7)	4.7 (2.4-23.7)	0.953
C-reactive protein, mg/L	2.0 (0.5 – 63)	2.0 (0.5 -92)	0.164

* P values obtained using Mann-Whitney / Wilcoxon rank sum tests

The proportion of participants who had all parameters within the reference interval, or an increasing number of parameters outside the reference intervals, was very similar between the two groups (Table 10.5). The two study groups were equally likely to fall in to the category '1-2 outside the reference interval', for biochemical test results. The mean (SD) of test results outside the reference interval was similar in both groups {Gulf War 1.13 (0.94) vs comparison group 1.15 (0.98), crude difference between the means 0.99, adjusted difference between the means 0.99; 95% CI 0.93-1.06, p=0.833}.

Similar proportions of the two groups fell within, and higher or lower than, the reference intervals for most of the individual biochemical test parameters. Gulf War veterans were more likely than comparison group subjects to have results outside and above the reference interval for sodium and creatinine.

A random blood glucose was used to compare study groups for an elevated blood glucose, because routinely obtaining a fasting plasma glucose was not possible for logistical reasons. Although IMVS routinely reports a fasting blood glucose interval, IMVS does not report a reference interval for a random blood glucose because it is very difficult to define what is "normal". Therefore, to compare study groups, the criteria used and the interpretation of these are those recently recommended by the NHMRC (http://www.health.gov.au/nhmrc/advice/pdf/type2.pdf). The two study groups demonstrated similar patterns of random blood glucose. More than 80% of participants in both study groups had a random blood glucose <5.5 mmol/L, which suggests that diabetes mellitus is unlikely in these participants. Approximately 15% of participants in both study groups had a random blood glucose in the range of 5.5-11.0 mmol/L which suggests these participants may be at risk of diabetes mellitus if they have other risk factors, but further testing would be needed to confirm this. Less than 1% of participants in both study groups had a random blood glucose >11.0 mmol/L (an elevated random blood glucose) which suggests that Type 2 diabetes mellitus is likely in these participants, but further testing would be needed to confirm this.

Table 10.5 Prevalences and ORs of biochemical test result analysed in relation to reference intervals

	GWV N=1369		Comp grp N=1379					
Analyte	**n**	**(%)**	**n**	**(%)**	**Crude OR**	**Adj OR**	**95% CI**	**P value**
Urea and electrolytes (U&Es)								
All within ref intervals	409	(29.9)	419	(31.0)	-	-	-	-
1-2 outside ref interval	857	(61.8)	819	(60.6)	-	-	-	-
≥ 3 outside ref interval	102	(7.5)	113	(8.4)	-	-	-	-
Sodium								
within ref interval (137-145 mmol/L)	1317	(95.6)	1324	(96.7)	-	-	-	-
<137 mmol/L	5	(0.4)	14	(1.0)	0.4	0.4	0.1-1.1	0.064
>145 mmol/L	56	(4.1)	31	(2.3)	1.8	1.8	1.1-2.8	0.011
Potassium								
within ref interval (3.8-4.9 mmol/L)	1310	(95.7)	1280	(94.7)	-	-	-	-

Analyte	GWV N=1369 n	(%)	Comp grp N=1379 n	(%)	Crude OR	Adj OR	95% CI	P value
<3.8 mmol/L	4	(0.3)	7	(0.5)	0.6	0.5	0.1-1.8	0.303
>4.9 mmol/L	55	(4.0)	64	(4.7)	0.8	0.9	0.6-1.3	0.547
Urea and creatinine								
Urea within ref interval (2.7-8.0 mmol/L)	1344	(97.6)	1330	(97.3)	-	-	-	-
Urea >8.0 mmol/L	30	(2.2)	30	(2.2)	1.0	1.0	0.6-1.7	0.977
Creatinine within ref interval (0.05-0.12 mmol/L)	1355	(98.4)	1360	(99.5)	-	-	-	-
Creatinine >0.12 mmol/L	20	(1.5)	7	(0.5)	2.9	3.1	1.3-7.4	0.012
Both urea and creatinine >ref interval	1	(0.1)	0	(0)	-	-	-	-
Ionised calcium and phosphate								
Ionised calcium within ref interval (1.10-1.25 mmol/L) *	1199	(87.9)	1206	(88.4)	-	-	-	-
<1.10 mmol/L	152	(11.1)	138	(10.1)	1.1	1.1	0.8-1.4	0.560
>1.25 mmol/L	13	(1.0)	20	(1.5)	0.7	0.6	0.3-1.3	0.201
Phosphate within ref interval (0.65-1.45 mmol/L)	1338	(97.1)	1325	(96.9)	1.0	0.9	0.3-2.7	0.782
Both ionised calcium and phosphate within ref intervals	1163	(85.3)	1168	(85.6)	0.9	0.9	0.6-1.5	0.748
Random plasma glucose								
5.5-11.0 mmol/L	226	(16.4)	211	(15.5)	-	-	-	-
<5.5 mmol/L	1137	(82.8)	1137	(83.7)	0.9	1.0	0.8-1.2	0.668
>11.0 mmol/L	11	(0.8)	10	(0.7)	1.0	1.1	0.5-2.7	0.836
C-Reactive Protein (CRP)								
within ref interval (<4-10 mg/L)	1323	(96.0)	1329	(97.1)	-	-	-	-
>10 mg/L	55	(4.0)	40	(2.9)	1.4	1.3	0.9-2.0	0.206

* Ionised calcium is adjusted for albumin and pH
† U&Es include sodium, potassium, chloride, bicarbonate, anion gap, ionised calcium and phosphate (but not urea and creatinine which are reported separately). Potassium results for which the potassium was >6 mmol/L and the renal function was normal (creatinine $\leq$ 0.12mmol/L) were excluded from the results because the potassium results were determined to be artefactually elevated, most often as a result of specimen deterioration due to the time elapsed between collection of the specimen and analysis.

10.4.2.3 Liver function test results

Table 10.6 shows that the mean (or median) values for the liver function test results were very similar for the two study groups.

Table 10.6 Mean (SD) or median (range) of liver function test results

Parameter	GWV N=1365 mean (SD)	Comp grp N=1365 mean (SD)	P value*
Albumin, g/L	42.2 (2.7)	42.0 (2.7)	0.039
Globulin, g/L	29.5 (3.8)	29.2 (3.7)	0.111
Total protein, g/L	71.7 (4.1)	71.3 (4.0)	0.007
	median (range)	**median (range)**	
Total bilirubin, μmol/L	10 (1-60)	10 (1-73)	0.001
GGT, U/L	26 (8-773)	26 (7-990)	0.542
ALP, U/L	74 (23-181)	73 (28-187)	0.099
ALT, U/L	28 (6-354)	29 (4-238)	0.858
AST, U/L	28 (7-155)	28 (10-450)	0.272

* P values obtained using Mann-Whitney / Wilcoxon rank sum tests

Furthermore, the proportion of participants from each group who had all parameters within, higher or lower than the reference intervals for individual parameters, or an increasing number of parameters outside the reference intervals, was very similar (Table 10.7). Gulf War veterans were not at increased risk of having more results outside the reference interval. The proportion with parameters outside the reference intervals fell smoothly above the '1-2 outside the reference interval' category. The mean (SD) of liver function test results outside the reference interval was similar in both groups {Gulf War veterans 0.64 (0.91) vs comparison group 0.63 (0.91), crude difference between means 1.02, adjusted difference between means 1.0; 95% CI 0.90-1.12, P=0.995}.

Table 10.7 Prevalences and ORs for liver function test results in relation to reference intervals

	GWV		Comp grp					
Parameter	**n**	**(%)**	**n**	**(%)**	**Crude OR**	**Adj OR**	**95% CI**	**P value**
Liver function tests (LFTs)								
All within ref intervals	790	(57.4)	800	(58.4)	-	-	-	-
1-2 outside ref interval	519	(37.7)	504	(36.8)	-	-	-	-
≥3 outside ref interval	68	(4.9)	65	(4.7)	-	-	-	-
Albumin								
within ref interval (34-48 g/L)	1364	(99.0)	1352	(98.8)	-	-	-	-
<34 g/L	0	(0)	3	(0.2)	0.0	0.0	-	-
>48 g/L	14	(1.0)	14	(1.0)	1.0	0.9	0.4-2.0	0.852
Globulin								
within ref interval (26-41 g/L)	1185	(86.0)	1163	(85.0)	-	-	-	-
<26 g/L	184	(13.4)	199	(14.5)	0.9	0.9	0.7-1.2	0.531
>41 g/L	9	(0.7)	7	(0.5)	1.3	1.4	0.5-3.7	0.543
Total protein								
within ref interval (65-85 g/L)	1333	(96.7)	1310	(95.7)	-	-	-	-
<65 g/L	44	(3.2)	55	(4.0)	0.8	0.8	0.5-1.2	0.301
>85 g/L	1	(0.1)	4	(0.3)	0.3	0.2	0.02-2.0	0.178
Total bilirubin								
within ref interval (6-24 μmol/L)	1249	(90.6)	1257	(91.8)	-	-	-	-
>24 μmol/L	53	(3.8)	57	(4.2)	0.9	1.0	0.7-1.5	0.970
GGT								
within ref interval (0-60 U/L)	1248	(90.6)	1235	(90.2)	-	-	-	-
>60 U/L	130	(9.4)	134	(9.8)	1.0	0.9	0.7-1.2	0.584
ALP								
within ref interval (30-110 U/L)	1295	(94.0)	1300	(95.0)	-	-	-	-
>110 U/L	80	(5.8)	68	(5.0)	1.2	1.1	0.8-1.6	0.487
ALT								
within reference interval (0-55 U/L)	1206	(87.5)	1227	(89.6)	-	-	-	-
>55 U/L	172	(12.5)	142	(10.4)	1.2	1.2	0.9-1.5	0.181
AST								
within ref interval (0-45 U/L)	1286	(94.3)	1292	(94.7)	-	-	-	-
>45 U/L	78	(5.7)	73	(5.3)	1.1	1.0	0.7-1.4	0.946

Of particular note were the liver enzyme test results. A higher than expected, but similar, proportion of GGT and ALT results between the two study groups, and to a lesser extent, proportion of ALP and AST results, were higher than the reference intervals. To investigate these results further, we examined combinations of elevated parameters that may indicate underlying liver disease (Table 10.8).

A combination of raised AST and ALT can be indicative of hepatitis (inflammation of the liver) regardless of the aetiology. A raised GGT in combination with a raised ALP can indicate an obstructive pattern of liver disease. A raised GGT in combination with a raised ALT can be indicative of viral hepatitis. GGT was raised in combination with ALT in 4.9% of Gulf War veterans and 4.3% of the comparison group. The proportion of Gulf War veterans with each of these combinations was slightly greater than that of the comparison group, however the odds ratios were not significantly increased (Table 10.8).

An abnormal bilirubin can be indicative of any type of liver disease, and an elevated bilirubin in combination with an elevation of one other liver enzyme is suggestive of underlying liver disease. Very small numbers in both study groups had a raised bilirubin in combination with other liver enzymes, and no Gulf War veterans had an elevated bilirubin in combination with ALP. None of the odds ratios were significantly increased.

Table 10.8 Prevalences and ORs for combinations of elevated liver enzymes

Combination of parameters	GWV		Comp grp					
	n	(%)	n	(%)	Crude OR	Adj OR	95% CI	P value
AST and ALT >ref interval	58	(4.3)	54	(4.0)	1.1	1.0	0.7-1.5	0.984
GGT and ALP >ref interval	22	(1.6)	14	(1.0)	1.6	1.6	0.8-3.1	0.208
GGT and AST >ref interval	36	(2.6)	28	(2.1)	1.3	1.2	0.7-1.9	0.563
GGT and ALT >ref interval	67	(4.9)	59	(4.3)	1.1	1.1	0.8-1.6	0.635
Bilirubin and GGT >ref interval	1	(0.1)	4	(0.3)	0.3	nc*	nc	nc
Bilirubin and ALP >ref interval	0	(0.0)	4	(0.3)	0.0	nc	nc	nc
Bilirubin and AST >ref interval	4	(0.3)	4	(0.3)	1.0	nc	nc	nc
Bilirubin and ALT >ref interval	4	(0.3)	6	(0.4)	0.7	0.7	0.2-2.5	0.564

* nc = not calculable

Very small numbers of participants had a positive hepatitis C core Ab status in conjunction with elevated levels of ALT {5 (0.1%) Gulf War veterans and 1 (0.1%) of the comparison group}, AST {3 (0.2%) Gulf War veterans and none of the comparison group} or bilirubin {none of the Gulf War veterans or comparison group}. This suggests that hepatitis C status was not an explanation for these raised liver function test parameters.

10.4.2.4 Serological test results

Table 10.9 shows the prevalences and ORs for the serological test results, which are similar in the Gulf War veteran and comparison group.

Table 10.9 Prevalences and ORs for serological test results

Parameter	GWV		Comp grp					
	n	(%)	n	(%)	Crude OR	Adj OR	95% CI	P value
Epstein-Barr virus antibody test, IgG Ab								
Not detected, Δsample < 0.100	56	(4.1)	65	(4.8)	-	-	-	-
Equivocal, 0.100 - 0.200	48	(3.5)	31	(2.3)	1.8	1.6	0.9-2.8	0.132
Detected, Δsample >0.200	1274	(92.5)	1270	(93.0)	1.2	1.1	0.7-1.5	0.797
Cytomegalovirus antibody test, IgG Ab								
Not detected, <10 AU/ml	671	(48.7)	666	(48.8)	-	-	-	-
Equivocal, 10-15 AU/ml	3	(0.2)	8	(0.6)	0.4	0.3	0.1-1.2	0.089
Detected, >15 antibody units/ml (AU/ml)	704	(51.1)	692	(50.7)	1.0	1.1	0.9-1.2	0.487
Hepatitis C serology, hepatitis C core Ab								
Negative, S/CO <1.00	1367	(99.2)	1352	(98.9)	-	-	-	-
Indeterminate, S/CO 0.80-0.99	0	(0)	6	(0.4)	0.0	0.0	-	-
Positive, S/CO >=1.00	11	(0.8)	9	(0.7)	1.2	1.2	0.5-3.0	0.683

10.4.2.5 Urinalysis results

Urinalysis was performed by the HSA nurse during the medical assessment. Table 10.10 shows the urinalysis results. Urinalysis testing was performed by colorimetric assessment, and therefore there may have been some interobserver variability. 'Traces' are not considered 'normal' while '1-4+, positive or small-large' are considered definitely abnormal. The Gulf War and comparison groups were not significantly different when compared for haematuria (blood in the urine), glycosuria (glucose in the urine), proteinuria (protein in the urine) or nitrites (which can indicate urinary infection). The proportions of both the Gulf War veteran and comparison group who had 1-4+ glycosuria was very similar, and similar to the proportions (0.8% vs 0.7%) that had an elevated random blood glucose. Although the numbers and proportion of participants who had positive results for blood or protein in their urine were small, these tests are not diagnostic and would generally require further investigation in clinical practice.

Table 10.10 Prevalences for urinalysis results

	GWV		Comp grp		
Parameter	**n**	**(%)**	**n**	**(%)**	**P value**
Protein					
Negative	1298	(94.0)	1303	(94.6)	p=0.435
Trace	70	(5.1)	58	(4.2)	
1-4+	13	(0.9)	17	(1.2)	
Blood					
Negative	1311	(94.9)	1306	(94.8)	p=0.878
Trace	44	(3.2)	48	(3.5)	
Small-large	26	(1.9)	24	(1.7)	
Glucose					
Negative	1365	(98.8)	1363	(98.9)	p=1.000*
Trace	2	(0.1)	1	(0.1)	
1-4+	14	(1.0)	14	(1.0)	
Nitrites					
Negative	1377	(99.8)	1369	(99.9)	p=0.625*
Positive	3	(0.2)	1	(0.1)	

* P value from Fisher's Exact test.

10.4.3 Gulf War veteran group subanalysis

Overall, the patterns of results for Gulf War veterans and the comparison group were very similar, and further subanalysis in relation to laboratory investigations and exposures in the Gulf War group was not undertaken.

10.5 Discussion

The laboratory investigations component of the study involved the collection of blood from 2810 consenting participants at 10 HSA offices and two additional medical assessment sites, and its national transportation to a single laboratory, IMVS, for analysis. A number of haematological, biochemical and serological tests were used to compare the Gulf War and comparison groups, and definitions for adverse health outcomes were developed in order to address the research questions of the study.

The data collection for this aspect of the study required considerable and sustained effort and attention to detail by those involved in order to achieve such a high level of data completeness and quality. The standardisation of results achieved by using one national laboratory in this study was of prime importance. In this study, bloods were transported nationally, albeit with a protocol for the initial processing and transportation of specimens in order to minimise any adverse effects on the specimens, and IMVS aimed to have all bloods tested within 24 hours. However, some parameters are more sensitive than others with respect to the time between blood collection and analysis, and artefact may be an explanation for the elevation of some parameters, such as ESR and MCV in both groups.

The main finding is that the patterns of results for the Gulf War veteran and comparison groups are similar for most parameters. There are minor differences between the study groups on two individual parameters only, with a greater proportion of Gulf War veterans having a sodium or creatinine above the reference interval. There is also a suggestion that liver enzymes were more likely to be elevated in Gulf War veterans, but not significantly. In all of these results, the prevalences were quite small and they need to be interpreted with caution. Also, the clinical significance for these parameters falling above the reference range is uncertain, but may indicate an early pre-clinical phase.

Some test results such as the MCV were elevated in both groups. The MCV tends to increase at the rate of approximately 6% in the first twenty-four hours (Personal communication with IMVS haematologist, August 2000), and artefactual elevation due to the time between blood collection and analysis may be an explanation for the elevated level of MCV in both study groups. This is likely to have affected both groups in a similar manner. High levels of alcohol consumption may also be an explanation. There are other causes of macrocytosis such as nutritional folate and vitamin B12 deficiency, which are less likely in these groups.

An elevated ESR has been reported elsewhere to be present in between 4 and 8 per cent of patients.[356] The ESR tends to decrease with time after collection. For example, an ESR performed at 24 hours may be up to 20% lower than the same test performed on a "fresh" specimen (Personal communication with IMVS haematologist, August 2000), and thus a higher proportion of both study groups may have had an ESR above the reference interval, but again this is likely to have affected both groups in a similar manner. In this regard, the high prevalence of ESR above the reference interval is difficult to explain, unless the strictly defined reference limits used were too simplistic a way of assessing this parameter.

An estimation of blood glucose in the groups was limited to a random blood glucose because of the logistical difficulties of collecting a fasting specimen in this study. Type 2 diabetes mellitus affects approximately 6% of the Australian population aged 25 or older, and 50% of these individuals are undiagnosed and largely asymptomatic. Although a similar and small proportion of the study groups have an elevated random blood glucose that suggests diabetes mellitus is likely, 16.4 % of Gulf War veterans and 15.5% of the comparison group have a random blood glucose which suggests they may be at risk of diabetes mellitus if they have other risk factors. Further testing would be needed to confirm this.

According to the definitions developed for this study, the study groups have a similar prevalence of a combination of parameters that may indicate inflammation. However, a limit in the further interpretation of this is the non-specific nature of the parameters themselves in relation to causes of inflammation such as infection, vasculitis, malignancy and others.

The seroprevalence of CMV, EBV and hepatitis C found in both study groups are comparable to those reported in the scientific and medical literature. CMV infection is common in all human populations, reaching 60-70% in urban US cities.[357] Antibodies to EBV have been found in all population groups studied. By adulthood, 90-95% of most populations have demonstrable EBV antibodies.[358] In developed nations, the hepatitis C prevalence is typically 1-2% of the general population,[359] ie similar to the rates found in this study. Risk factors for hepatitis C include tattoos, blood transfusions and intravenous drug use, but we do not have data on these latter two risk factors from this study.

Although the US and UK clinical evaluation programs undertook further investigations such as laboratory tests in order to establish diagnoses for the self-referred veterans, only one cross-sectional epidemiological study has reported a medical assessment as part of the study.

Ishoy *et al*[162] found minor differences between study groups. Of the parameters included in this study, Danish Gulf War veterans had a slightly elevated mean number of platelets {205 vs 211 x 10^9/l, p<.05}, a slightly lower eosinophil count (0.18 vs 0.20 x 10^9/l, P<0.01), and a very slightly elevated plasma creatinine (0.092 vs 0.091 mmol/l, P<.01). Of these previously reported findings, the only similar finding in our study was the significantly greater proportion of Gulf War veterans with an elevated creatinine.

We were unable to locate any published national Australian survey data for laboratory investigations (personal communication with Specialist Pathologist and Head, Diagnostic Services Laboratory, IMVS), and the generalisability of results from other studies may be limited because of the different testing methodologies used. Therefore, comparison of our results with those of the general population are limited to that achieved through the comparison of study groups using the IMVS reference intervals. Laboratory investigations are usually used to assess individuals in a clinical setting where a doctor wants to confirm, or exclude, possible diagnoses, but the use of reference intervals in this study provided a framework for comparing the study groups. The laboratory haematology, biochemistry and liver function test reference intervals were established by IMVS through the testing of 230 "laboratory normal" healthy individuals and comparing the results with those reported in the international scientific literature. Reference intervals have some limitations. The sample used by IMVS to develop their reference intervals was not representative of the general population. The high proportion of males in our study groups may mean that more than 2.5% of the groups would be expected to be outside the reference intervals. Results outside the reference intervals are not necessarily abnormal, and the comparisons made with the comparison group are very important in this respect.

Although the parameters used to compare the study groups in the analysis were decided *a priori*, a large number of analyses were undertaken to compare the two study groups on the laboratory test results, and this increases the risk of chance findings.

As part of the feedback of results to participants, a medical report was prepared by a HSA doctor who completed their medical assessment. This medical report was provided to each participant for follow up as required, and a copy was provided to their medical practitioner if they chose to nominate one.

10.5.1 Summary of findings

In summary, and in answer to the research questions, the laboratory investigation results of Gulf War veterans were very similar, with only minor differences between the study groups. The proportion of Gulf War veterans that are outside the reference intervals for individual parameters tends to be higher than the comparison group. Some of these differences may be due to artefact or due to technical difficulties.

Gulf War veterans do not have significantly more haematological test results that are indicative of anaemia or inflammation than the comparison group. A relatively high, but similar, proportion of Gulf War veterans and comparison group have haematological test results that are indicative of inflammation, according to the study definitions. The elevation of indicators of inflammation are based on non-specific parameters in both groups, and this finding may warrant further investigation in relation to possible exposure subgroups.

Gulf War veterans have a greater proportion of results that may indicate renal impairment, but the numbers are small and need to be interpreted with caution. Only one Gulf War veteran and no comparison group subjects had both urea and creatinine elevated (which is a more specific indicator of renal impairment). Gulf War veterans do not have more

biochemical tests results that are indicative of raised blood glucose than the comparison group. Gulf War veterans have slightly greater proportions of combinations of liver enzymes that may be indicative of liver disease than the comparison group, but the differences are not statistically significant.

Some of the differences found, such as the slightly greater proportions of combinations of liver enzymes indicating liver disease and a raised creatinine indicating renal disease may need to be investigated further on an individual basis. Alcohol consumption may be a cause of the elevation of some haematological or liver function test parameters in both groups, although other explanations are possible. The high proportion of both study groups that have a random blood glucose within a range that suggests they may be at risk of diabetes warrants follow-up and if they have other risk factors, may need to be investigated further on an individual basis.

Gulf War veterans do not have significantly more serological test results that are indicative of prior exposure to viral infections with Epstein-Barr virus (EBV), Cytomegalovirus (CMV) or hepatitis C than the comparison group.

Australian Gulf War veterans do not have more have more abnormalities on urinalysis testing when compared for haematuria (blood in the urine), glycosuria (glucose in the urine), proteinuria (protein in the urine) or nitrites (which can indicate urinary infection) than the comparison group.

11. Psychological health

11.1 Aim

The aim of the analysis in this chapter is to investigate whether Australian male Gulf War veterans have a different psychological health profile to that of the comparison group. Specifically the analysis aims to determine whether Gulf War veterans are more likely, than the comparison group, to have developed a psychological disorder since the time of the Gulf War. In addition, the analysis aims to determine whether Gulf War veterans are more likely than comparison group subjects to have psychological disorders which have been present in the previous twelve months. Where differences between the Gulf War veterans and comparison group subjects exist, this analysis aims to determine whether the differences are associated with age, service type, rank or other exposures and experiences that occurred as part of the Gulf War deployment.

The analysis also aims to explore the effects of possible participation bias on the results of the psychological health investigations.

11.2 Research questions

1. Are Australian Gulf War veterans more or less likely, than the comparison group, to develop a psychological disorder in the period following the Gulf War?
2. Are Australian Gulf War veterans more or less likely, than the comparison group, to have psychological disorders which have been present in the previous 12 months?
3. Do Australian Gulf War veterans score differently on the 12 item General Health Questionnaire when compared with the comparison group?
4. Do Australian Gulf War veterans score differently on the Posttraumatic Stress Disorder Checklist when compared with the comparison group?
5. Do Australian Gulf War veterans score differently on the Alcohol Use Disorders Identification Test when compared with the comparison group?
6. Where differences in risk of psychological disorders occur between Australian Gulf War veterans and the comparison group, are these associated with differences in exposures and experiences that occurred during the Gulf War deployment?

11.3 Methods and materials

The investigation of psychological health included administration of a comprehensive, psychologist-administered psychological health interview and several briefer, self-administered questionnaires.

11.3.1 Measurement of psychological health

A complete description of the instruments used in the assessment of psychological health is provided in chapter 5. The methods for scoring each instrument are defined below.

11.3.1.1 Composite International Diagnostic Interview, CIDI-Auto 2.1

The prevalence of several affective, anxiety, somatic and substance-use disorders was assessed according to diagnostic criteria described in the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders DSM-IV.[308] The instrument used was an interviewer administered version of the Composite International Diagnostic Interview, CIDI-Auto 2.1.[306] For each

participant, upon interview, the CIDI-Auto 2.1 output included whether a disorder had been present or absent and, for those disorders which had been present, the output included the age of first onset of symptoms (age of onset) and the age of last symptoms (age of recency). The CIDI output also included a recency code categorising the time period, prior to the interview, within which the most recent symptoms were experienced. These recency codes were:

1. within two weeks
2. two weeks to less than one month ago
3. one month to less than six months ago
4. six months to less than one year ago
5. in the last twelve months, don't know when
6. more than one year ago

Using the age of onset, age of recency and recency code the study team classified the present disorders in to the following categories:

- **CIDI defined DSM-IV pre-Gulf War disorder**: *all diagnosed disorders where age of onset of first symptoms was less than the subject's age at 1 August 1990.*

  Disorders included in this category were those which were first experienced by the subject prior to the time of the Gulf War. Age of recency was not considered in this definition; symptoms may have ceased prior to the Gulf War, or may have continued after the time of the Gulf War.

- **CIDI defined DSM-IV post-Gulf War disorder:** *all diagnosed disorders where age of onset of first symptoms was greater than or equal to the subject's age at 1 August 1990.*

  Disorders included in this category were those which were first experienced by the subject during or after the time of the Gulf War. Age of recency was not considered in this definition; symptoms may have ceased at any time since the Gulf War, or may have been ongoing at the time of assessment.

- **CIDI defined DSM-IV disorder present in previous 12 months**: *any pre-Gulf War or post-Gulf War disorder where symptoms have been present within twelve months of the interview.*

  Disorders included in this category were those pre-Gulf War and post-Gulf War disorders with recency codes 1 to 5; excluding those with code 6.

- **CIDI defined DSM-IV current disorder**: *any pre-Gulf War or post-Gulf War disorder where symptoms have been present within four weeks of the interview.*

  Disorders included in this category were those pre-Gulf War and post-Gulf War disorders with recency codes 1 and 2; excluding codes 3 to 6.

Age at 1 August 1990 was calculated by the study team and rounded down to whole years; for example, 35.7 years of age was truncated to 35 years of age.

It is important to note that the CIDI gives only age of onset of first symptoms, per person, per diagnosis and does not record remissions and subsequent onset of symptoms for the same diagnosis. Therefore, if age of onset for a diagnosis was less than the subject's age at 1 August 1990, the study team could only classify that disorder as "pre-Gulf War" regardless of whether new symptoms were experienced after the time of the Gulf War. For a subject to be categorised as having a particular "post-Gulf War disorder" they could not have had that same disorder categorised as "pre-Gulf War". All subjects with pre-Gulf War diagnoses were excluded from the analyses of post-Gulf War disorders of the same type.

11.3.1.2 12-item General Health Questionnaire (GHQ-12)

The GHQ-12 was scored by coding the four possible responses to each question as 0 – 0 – 1 – 1 and then summing the binary scores.[218] Respondents were given a total score ranging from a minimum of zero to a maximum of twelve, with a higher score indicating poorer psychological health.

Several thresholds, or cut-off scores, for determining GHQ-12 caseness, or possible psychiatric condition, have been employed in the literature.[264, 271] Using the ANSHWB data, Donath reported an optimum threshold of one or more symptoms for the Australian population.[269] Earlier Australian studies have reported optimum cut off scores of two or more[360] and as high as eight or more.[268] These extremes have been observed by Goldberg[264] in a comparison of GHQ-12 screening threshold results across fifteen cities. In their studies of British Gulf War veterans, the King's College Group employed a GHQ-12 caseness score of three or more symptoms.[21, 155]

To determine the most appropriate GHQ-12 caseness score in our study, Receiver Operating Characteristic (ROC) analysis[361] was conducted to identify the GHQ-12 score with the best specificity and sensitivity to detect a person with or without any current psychological disorder (as defined using the CIDI and present within the previous four weeks), excluding current substance use disorder, alcohol use disorder and specific phobia. For each possible cut-point (for example, 1, 2 or 3 symptoms and so on), the sensitivity (Y-axis) and 1-specificity,[362] otherwise known as the false positive rate (X-axis), were calculated and plotted. The area under the resulting plotted ROC curve represented the probability that a randomly chosen subject with any current psychological disorder would have a higher GHQ-12 score than a randomly chosen subject without any current psychological disorder. The method for constructing the area under the ROC curve, and the confidence interval, is described by Hanley and McNeil.[363]

Using ROC analysis, and assuming equal importance of sensitivity and specificity, the optimum cut-off point for the GHQ-12 in our study proved to be two symptoms, with sensitivity 0.73 (95% CI = 0.67 to 0.77) and specificity 0.68 (95% CI =0.66 to 0.69). The area under the curve was 0.77 (95% CI 0.74 to 0.80). The method used to calculate confidence intervals for sensitivity and specificity, was described by McKenzie *et al*[364] and was conducted using the software of Mackinnon.[365]

11.3.1.3 Posttraumatic Stress Disorder Checklist-S (PCL-S)

The PCL-S is one of three versions of the Posttraumatic Stress Disorder Checklist (PCL) available.[278] The same standard scoring method applies to each version of the PCL with a total score computed by coding the five possible responses to each question as 1 – 2 – 3 – 4 – 5 and then summing the results. With seventeen questions in total, possible scores range from 17 to 85. In our study the cut-off score for PCL-S caseness, predictive of possible posttraumatic stress disorder, was set at ≥50. This threshold was recommended by Weathers[278] and was shown to have a sensitivity of 0.82 and a specificity of 0.83 in predicting posttraumatic stress disorder cases as measured using the Structured Clinical Interview for DSM-III-R in Vietnam War veterans. In their study of the validity of the PCL as a measure of symptomatic change in Australian veterans of the Vietnam War with current posttraumatic stress disorder, Forbes *et al* supported the use of the diagnostic cut-off of ≥50, which had a sensitivity of 0.97[366] (specificity was not applicable as all subjects had posttraumatic stress disorder).

11.3.1.4 Alcohol Use Disorders Identification Test (AUDIT)

The AUDIT was scored by coding the five possible responses to questions 1-8, as 0 – 1 – 2 – 3 – 4, and coding the three possible responses to questions 9-10 as 0 – 2 – 4. The ten items were then summed to result in a total score ranging from 0 to 40.[367]

In our study the cut-off score for AUDIT caseness, predictive of problem drinking, was set at ≥8 as recommended by the WHO.[276] Bohn *et a*[367] used ROC analysis to investigate different AUDIT thresholds for optimal detection of alcohol risk groups. They found that an AUDIT score of ≥8 could detect 98% (0.98) of hazardous drinkers; that is, drinkers who have not yet experienced alcohol-related problems, yet consume alcohol in patterns that increase the risk of developing such problems. Specificity for the ≥8 threshold, for hazardous drinkers, was only 34% (0.34). In the detection of harmful drinkers, defined as those who experience physical or mental harm due to drinking, but who are not alcohol dependent, the AUDIT threshold of ≥8 showed sensitivity of 0.77 and specificity of 0.81. Bohn *et al*, however, recommended the use of a ≥10 threshold, which demonstrated poorer sensitivity of 0.87 in hazardous drinkers and 0.60 in harmful drinkers, but improved specificity of 0.75 and 0.87 respectively.[367]

Barry and Fleming[277] reported that an AUDIT score of ≥5 represented the optimal balance between sensitivity and 1-specificity, on their ROC curve, for the detection of drinkers who met lifetime DSM-III criteria for alcohol misuse and or dependence. To minimise the possibility of false positive tests, however, these authors recommended raising the cut-off score to 7 or 8.

11.3.2 Gulf War exposure measures

Where differences in risk of psychological disorders exist between Gulf War veterans and the comparison group, the analysis will investigate associations with several measures of exposure.

Specifically, the analysis will investigate whether risk of psychological disorders in either study group differs across subcategories of age, service type and rank.

Further, the analysis will investigate whether a difference in risk of psychological disorders exists between Gulf War veterans and those comparison group subjects who have been on other active deployments.

Finally the analysis will investigate whether risk of psychological disorders within the Gulf War veteran group differs according to:

- Military Service Experience questionnaire score
- Deployment completed before or after the air war commenced on 17 January 1991
- Total number of immunisations

The scoring and groupings for these exposures are described in chapter 8.

11.4 Results

11.4.1 CIDI-defined DSM-IV disorders

Subjects included in the analysis of CIDI-defined DSM-IV psychological disorders were all those males who completed the interviewer administered psychological assessment. These included 1381 Gulf War veterans and 1377 comparison group subjects. They represented 99.8% of male subjects, from both groups, who attended HSA for the study's medical examination.

The results for Gulf War veterans and comparison group subjects who met criteria for CIDI-defined pre-Gulf War disorders, are shown in Table 11.1. Prevalence across groups for most

pre-Gulf War disorders were similar, indicating that the two groups varied little in their overall levels of psychological morbidity prior to the time of the Gulf War deployment.

The results for Gulf War veterans and comparison group subjects, who met criteria for CIDI-defined post-Gulf War disorders, are also shown in Table 11.1. The results for CIDI-defined disorders present within the previous 12 months are presented in Table 11.2.

Gulf War veterans were more likely than the comparison group to develop most post-Gulf War psychological disorders. Of particular note, the risk of several post-Gulf War anxiety disorders including posttraumatic stress disorder, obsessive compulsive disorder and social phobia, was elevated three to five times in Gulf War veterans. Increased risk for post-Gulf War bipolar disorder was almost three fold, and risk for post-Gulf War major depression, alcohol dependence or abuse and drug dependence or abuse were all more than one and a half times higher in Gulf War veterans. These increased risks remained statistically significant after adjustment for service type, rank, age, education level and marital status. Only when numbers were small, and prevalences were around one percent or less, did the increased risk in Gulf War veterans not reach statistical significance for post-Gulf War disorders.

Alcohol dependence and abuse and major depression were the most prevalent post-Gulf War disorders in both groups. The overall levels of post-Gulf War somatic disorders were very low, affecting less than one percent of all subjects. No subjects recorded a diagnosis of somatisation disorder.

In relation to CIDI defined disorders present within the previous 12 months (Table 11.2), anxiety disorders including posttraumatic stress disorder, obsessive compulsive disorder, social phobia and panic disorder and agoraphobia, were three to five times more likely in Gulf War veterans. These associations persisted after adjustment for the presence of the disorders prior to the Gulf War, in addition to the adjustments for service type, rank, age, education level and marital status. Bipolar disorder was more than two times more likely in Gulf War veterans, and major depression and alcohol dependence or abuse were more than one and a half times more likely when assessed as present within the previous 12 months.

Gulf War veterans were also more likely than the comparison group to have more than one CIDI disorder present within the previous 12 months, with 7% of Gulf War veterans and 3.5% of the comparison group recording two or more of these disorders. On average, Gulf War veterans had two times as many disorders present in the previous 12 months as the comparison group.

In both groups, subjects with '*any affective disorder'* primarily comprised those with a major depression and subjects with '*any substance use disorder'* primarily comprised those with alcohol dependence or abuse.

Table 11.1 Lifetime CIDI-defined DSM-IV disorders first present prior to the Gulf War, and those newly present after the Gulf War, in male Gulf War veterans and comparison group subjects.

CIDI-defined DSM-IV disorder	Disorder first present pre-Gulf War				Disorder first present post-Gulf War							
	Gulf War veterans (N=1381)		Comparison group (N=1377)		Gulf War veterans†		Comparison group†					
	n	(%)	n	(%)	n	(%)†	n	(%)†	OR	adj OR‡	CI	P value
Any affective disorder	**37**	**(2.7)**	**40**	**(2.9)**	**250**	**(18.6)**	**164**	**(12.3)**	**1.6**	**1.7**	**1.3-2.1**	**<0.001**
Major depression[a]	32	(2.3)	35	(2.5)	225	(16.7)	152	(11.3)	1.6	1.6	1.3-2.0	<0.001
Dysthymia	4	(0.3)	4	(0.3)	5	(0.4)	4	(0.3)	1.2	1.4*	0.3-7.2	0.912
Bipolar disorder[b]	2	(0.1)	1	(0.1)	25	(1.8)	9	(0.7)	2.8	2.7	1.2-5.9	0.013
Any anxiety disorder	**113**	**(8.2)**	**86**	**(6.2)**	**105**	**(8.3)**	**40**	**(3.1)**	**2.8**	**2.9**	**2.0-4.2**	**<0.001**
Posttraumatic stress disorder	18	(1.3)	17	(1.2)	73	(5.4)	19	(1.4)	4.0	3.9	2.3-6.5	<0.001
Generalised anxiety disorder	1	(0.1)	0	(0)	10	(0.7)	3	(0.2)	3.3	2.9*	0.7-16.4	0.165
Obsessive-Compulsive disorder	10	(0.7)	6	(0.4)	18	(1.3)	4	(0.3)	4.5	5.6*	1.7-24.2	0.002
Specific phobia	60	(4.3)	54	(3.9)	11	(0.8)	9	(0.7)	1.2	1.2	0.5-2.9	0.700
Social phobia	19	(1.4)	12	(0.9)	35	(2.6)	12	(0.9)	3.0	3.1	1.6-6.0	0.001
Panic disorder/Agoraphobia	13	(0.9)	4	(0.3)	12	(0.9)	6	(0.4)	2.0	2.5	0.8-7.2	0.097
Any somatic disorder	**14**	**(1.0)**	**7**	**(0.5)**	**18**	**(1.3)**	**8**	**(0.6)**	**2.3**	**1.9**	**0.8-4.5**	**0.138**
Somatisation disorder	0	(0)	0	(0)	0	(0)	0	(0)	-	-	-	-
Conversion disorder	7	(0.5)	1	(0.1)	6	(0.4)	1	(0.1)	6.0	4.4*	0.5-21.3	0.295
Pain disorder	2	(0.1)	3	(0.2)	3	(0.2)	2	(0.1)	1.5	1.4*	0.2-16.4	1.000
Hypochondriasis	6	(0.4)	3	(0.2)	9	(0.7)	5	(0.4)	1.8	1.6*	0.5-6.0	0.600
Any substance use disorder	**350**	**(25.3)**	**394**	**(28.6)**	**214**	**(20.8)**	**129**	**(13.1)**	**1.7**	**1.5**	**1.2-2.0**	**0.001**
Alcohol dependence/abuse[c]	327	(23.7)	384	(27.9)	209	(19.8)	125	(12.6)	1.7	1.5	1.2-2.0	0.001
Drug dependence/abuse[c]	38	(2.8)	32	(2.3)	50	(3.7)	24	(1.8)	2.1	1.9	1.1-3.2	0.015
Any CIDI disorder	**430**	**(31.1)**	**464**	**(33.7)**	**425**	**(30.8)**	**290**	**(21.1)**	**1.7**	**1.6**	**1.3-1.9**	**<0.001**

† The value of N, from which each percentage is derived, varies for each disorder and is the number of subjects who did not already have a pre-Gulf War diagnosis of the same type of disorder

‡. Odds ratios are adjusted for service type, rank and age (< 20, 20-24, 25 to 34, ≥35 years), education and marital status.

* Where numbers were small, odds ratios are adjusted for service type, rank and age (<25 vs ≥25 years) only. CI and P values for these adjusted odds ratios were obtained using exact methods for stratified 2x2 tables

a. 'Major depression single episode' and 'Major depression recurrent' combined b. 'Bipolar depressed' and 'Bipolar manic' combined c. Dependence and Abuse combined

Table 11.2 CIDI-defined DSM-IV disorders present within 12 months prior to assessment, in male Gulf War veterans and comparison group subjects.

Disorder present within previous 12 months								
	Gulf War veterans (N=1381)		**Comparison group (N=1377)**					
CIDI-defined DSM-IV disorder	**n**	**(%)**	**n**	**(%)**	**Crude OR**	**Adj OR‡**	**95% CI**	**P value**
Any affective disorder	**144**	**(10.4)**	**88**	**(6.4)**	**1.7**	**1.7**	**1.2-2.2**	**0.001**
Major depression[a]	124	(9.0)	76	(5.5)	1.7	1.7	1.2-2.3	0.001
Dysthymia	3	(0.2)	5	(0.4)	0.6	0.5*	0.1-2.8	0.574
Bipolar disorder[b]	19	(1.4)	8	(0.6)	2.4	2.2	0.9-5.4	0.071
Any anxiety disorder	**177**	**(12.8)**	**98**	**(7.1)**	**1.9**	**2.2**	**1.6-3.2**	**<0.001**
Posttraumatic stress disorder	71	(5.1)	23	(1.7)	3.2	4.1	2.4-7.2	<0.001
Generalised anxiety disorder	6	(0.4)	2	(0.1)	3.0	2.6*	0.5-27.0	1.000
Obsessive-Compulsive disorder	24	(1.7)	7	(0.5)	3.5	5.2	1.6-16.7	0.005
Specific phobia	53	(3.8)	54	(3.9)	1.0	0.7	0.3-1.4	0.335
Social phobia	50	(3.6)	17	(1.2)	3.0	3.4	1.7-6.6	<0.001
Panic disorder/Agoraphobia	21	(1.5)	7	(0.5)	3.0	3.3	1.1-10.2	0.034
Any somatic disorder	**28**	**(2.0)**	**10**	**(0.7)**	**2.8**	**2.6**	**1.0-6.3**	**0.041**
Somatisation disorder	0	0	0	0	-	-	-	-
Conversion disorder	13	(0.9)	2	(0.1)	6.5	4.4*	0.5-21.2	0.295
Pain disorder	5	(0.4)	4	(0.3)	1.2	1.4*	0.2-16.4	1.000
Hypochondriasis	11	(0.8)	4	(0.3)	2.8	2.4*	0.6-11.8	0.278
Any substance use disorder	**67**	**(4.9)**	**41**	**(3.0)**	**1.7**	**1.6**	**1.1-2.5**	**0.019**
Alcohol dependence/abuse[c]	60	(4.3)	34	(2.5)	1.8	1.8	1.1-2.8	0.011
Drug dependence/abuse[c]	9	(0.7)	8	(0.6)	1.1	0.8*	0.3-2.5	0.863
Any CIDI disorder	**284**	**(20.6)**	**188**	**(13.7)**	**1.6**	**1.7**	**1.4-2.1**	**<0.001**
One CIDI disorder	186	(13.5)	139	(10.1)	-	-	-	-
Two CIDI disorders	49	(3.5)	36	(2.6)	-	-	-	-
Three or more CIDI disorders	49	(3.5)	13	(0.9)	-	-	-	-
	Mean	**(SD)**	**Mean**	**(SD)**	**Ratio of means**	**Adj Ratio of means**	**95% CI**	**P value**
Mean number of disorders	0.34	(0.84)	0.18	(0.51)	1.9	1.9	1.5-2.3	<0.001

‡. Odds ratios are adjusted for service type, rank and age (< 20, 20-24, 25 to 34, ≥35 years), education, marital status and pre-Gulf War disorders of the same type.

* Where numbers were small, odds ratios are adjusted for service type, rank and age (<25 vs ≥25 years) only. CI and P values for these adjusted odds ratios were obtained using exact methods for stratified 2x2 tables

a. 'Major depression single episode' and 'Major depression recurrent' combined

b. 'Bipolar depressed' and 'Bipolar manic' combined

c. Dependence and Abuse combined

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Table 11.3 through to Table 11.6 demonstrate the effects of study group (Gulf War veterans versus comparison group) upon several categories of CIDI defined post-Gulf War psychological disorder, across subgroups of age, service type and rank. The disorders considered were 'any affective disorder', 'any anxiety disorder', posttraumatic stress disorder and 'any substance use disorder'. Age, service type and rank serve as proxies for potentially differing levels of experience and exposures. P values for interaction assessed whether the adjusted odds ratios were consistent across the subgroups of age, service type and rank.

Within almost every subgroup of age, service type and rank, Gulf War veterans had higher prevalences than the comparison group in each of the presented categories of CIDI defined post-Gulf War disorder. Many of these differences between the two groups, and within the subgroups of age, service type and rank, remained statistically significant after adjustment for the other subgroups, with the exception of differences between the two groups in substance use disorders. There was only a small amount of variation in the adjusted odds ratios across subgroups of age, service type and rank and tests for interaction failed to reach statistical significance. This indicates that the Gulf War deployment did not affect one subgroup differently to another. For example, the Gulf War deployment is associated with increased post-Gulf War affective disorders in Gulf War veterans, however the Gulf War deployment is not more strongly associated with increasing affective disorders in < 20 year olds than it is in increasing affective disorders in ≥35 year olds. This finding held for anxiety disorders, posttraumatic stress disorder and substance use disorders, and also for the different subgroups of service type and rank.

Subjects classified as 'other ranks-non supervisory', compared with 'other ranks-supervisory' and 'officer' ranks, demonstrated the highest prevalences of psychological disorder, for both study groups and for all broad categories of post-Gulf War disorder. For most disorder categories, prevalences amongst non-supervisory ranks in both groups were approximately twice as high as prevalences amongst officer ranks. The prevalences of post-Gulf War substance-use disorders, in both study groups, were more than six times higher in the non-supervisory ranks than in the officer ranks. Officer ranks were found to have the lowest prevalences in all but one disorder category, with the single exception of posttraumatic stress disorder, for which supervisory ranks showed the lowest prevalence. The Gulf War deployment, however, was no more associated with increasing risk in the lower rank subgroups, than it was with increasing risk in higher rank subgroups.

Subjects aged <25 years in both study groups, generally recorded more substance use disorders and more affective disorders than subjects aged ≥25 years. For these and other disorders however, the Gulf War deployment did not increase risk in one subgroup of age differently to another.

In relation to service type, post-Gulf War psychological disorders were generally least prevalent amongst Air Force participants in both study groups. Post-Gulf War affective disorders and anxiety disorders were most prevalent in Army participants in both groups when compared with the other services. In contrast, post-Gulf War substance use disorders were most prevalent in Navy subjects in both study groups when compared with the other services. There were no differences in the effect of the Gulf War deployment across the service types.

Table 11.3 Any post-Gulf War affective disorder: The effects of study group across subgroups of age, service type and rank.

	GWV		Comp grp					
	N	**(%)**	**n**	**(%)**	**Crude OR**	**Adj OR†**	**95% CI**	**P value‡**
Age								
< 20	38	(22.4)	13	(11.7)	2.2	2.2	1.1-4.5	
20-24	92	(23.7)	53	(15.7)	1.7	1.7	1.1-2.5	
25-34	94	(15.0)	76	(11.0)	1.4	1.5	1.1-2.1	0.756
≥ 35	26	(16.5)	22	(11.1)	1.6	1.9	1.0-3.5	
Service Type								
Navy	218	(18.6)	123	(12.4)	1.6	1.6	1.3-2.1	
Army	17	(21.3)	21	(14.2)	1.6	1.6	0.8-3.4	0.921
Air Force	15	(16.7)	20	(10.1)	1.8	1.9	0.9-4.0	
Rank								
Officer	32	(12.9)	27	(8.3)	1.6	1.8	1.1-3.2	
Other rank-supervisory	104	(16.1)	83	(12.6)	1.3	1.4	1.0-1.9	0.368
Other rank-non supervisory	113	(25.1)	54	(15.3)	1.9	2.0	1.4-2.9	

† Odds ratios are adjusted for service type, rank and age (< 20, 20-24, 25 to 34, ≥35 years), education and marital status
‡ P value for interaction

Table 11.4 Any post-Gulf War anxiety disorder: The effects of study group across subgroups of age, service type and rank.

	GWV		Comp grp					
	n	**(%)**	**n**	**(%)**	**Crude OR**	**Adj OR***	**95% CI**	**P value‡**
Age								
< 20	15	(9.3)	2	(1.8)	5.5	4.8	1.1-44.6	
20-24	36	(9.9)	13	(4.0)	2.6	2.6	1.3-5.5	
25-34	39	(6.6)	22	(3.3)	2.1	2.2	1.2-3.9	0.215
≥ 35	15	(9.8)	3	(1.6)	6.8	6.1	1.6-34.6	
Service Type								
Navy	90	(8.2)	30	(3.1)	2.7	2.7	1.7-4.2	
Army	12	(15.4)	7	(5.0)	3.5	3.9	1.3-12.6	0.934
Air Force	3	(3.4)	3	(1.5)	2.3	2.2	0.3-17.1	
Rank								
Officer	19	(7.9)	7	(2.1)	3.9	4.1	1.5-12.0	
Other rank-supervisory	38	(6.3)	20	(3.2)	2.0	2.1	1.2-4.0	0.540
Other rank-non supervisory	47	(11.1)	13	(3.8)	3.1	3.1	1.6-6.5	

* These odds ratios are adjusted for service type, rank and age (<25 vs ≥25 years) only. CI values for these adjusted odds ratios were obtained using exact methods for stratified 2x2 tables
‡ P value for interaction

Table 11.5 Any post-Gulf War posttraumatic stress disorder: The effects of study group across subgroups of age, service type and rank.

	GWV		Comp grp					
	n	**(%)**	**n**	**(%)**	**Crude OR**	**Adj OR***	**95% CI**	**P value‡**
Age								
< 20	9	(5.3)	1	(0.9)	6.2	4.9	0.6-222	
20-24	25	(6.4)	5	(1.5)	4.6	4.0	1.5-13.6	
25-34	25	(3.9)	12	(1.7)	2.3	2.2	1.0-4.9	0.100
≥ 35	14	(8.5)	1	(0.5)	18.7	16.9	2.4-729	
Service Type								
Navy	63	(5.3)	16	(1.6)	3.5	3.4	1.9-6.3	
Army	5	(6.0)	2	(1.3)	4.7	4.3	0.7-46.9	0.871
Air Force	5	(5.4)	1	(0.5)	11.8	8.3	0.9-40.6	
Rank								
Officer	11	(4.4)	2	(0.6)	7.6	6.6	1.4-63.1	
Other rank-supervisory	28	(4.3)	10	(1.5)	2.9	3.0	1.4-6.9	0.538
Other rank-non supervisory	33	(7.3)	7	(2.0)	3.9	3.9	1.7-10.6	

* These odds ratios are adjusted for service type, rank and age (<25 vs ≥25 years) only. CI values for these adjusted odds ratios were obtained using exact methods for stratified 2x2 tables.
‡ P value for interaction

Table 11.6 Any post-Gulf War substance-use disorder: The effects of study group across subcategories of age, service type and rank.

	GWV		Comp grp					
	n	**(%)**	**n**	**(%)**	**Crude OR**	**Adj OR†**	**95% CI**	**P value‡**
Age								
< 20	67	(42.9)	32	(34.0)	1.5	1.5	0.9-2.6	
20-24	77	(26.0)	43	(16.3)	1.8	1.7	1.1-2.7	
25-34	60	(13.0)	47	(9.5)	1.4	1.4	0.9-2.1	0.884
≥ 35	10	(8.5)	7	(5.3)	1.7	1.8	0.7-5.1	
Service Type								
Navy	202	(22.8)	110	(15.7)	1.6	1.6	1.2-2.1	
Army	9	(14.1)	9	(8.6)	1.7	1.6	0.6-4.4	0.382
Air Force	3	(3.7)	10	(5.7)	0.6	0.6*	0.1-2.7	
Rank								
Officer	12	(5.5)	11	(4.0)	1.4	1.3	0.6-3.0	
Other rank-supervisory	66	(14.4)	44	(10.4)	1.5	1.4	0.9-2.1	0.678
Other rank-non supervisory	135	(38.0)	74	(26.2)	1.7	1.7	1.2-2.5	

† Odds ratios are adjusted for service type, rank and age (< 20, 20-24, 25 to 34, ≥35 years), education and marital status
‡ P value for interaction
* Where numbers are small, odds ratios are adjusted for service type, rank and age (<25 vs ≥25 years) only. CI values for these adjusted odds ratios were obtained using exact methods for stratified 2x2 tables

11.4.2 12 item General Health Questionnaire (GHQ-12)

1422 (99.9%) Gulf War veterans and 1544 (99.7%) comparison group subjects completed the GHQ-12 in the postal questionnaire. Table 11.7 presents the prevalence of GHQ-12 cases (GHQ-12 symptom score ≥ 2) for all Gulf War veteran and comparison group subjects, and for all subjects within subgroups of age, service type and rank. Gulf War veterans were more likely than comparison group subjects to be suffering psychological morbidity as measured by this instrument. The difference between study groups remained statistically significant after adjustment for age, service type, rank, education and marital status.

There was a strong age effect, with younger Gulf War veterans having a greater prevalence of GHQ caseness than older Gulf War veterans, whilst in the comparison group prevalence was greatest in the oldest subjects. This indicates a differential age effect of Gulf War service upon increasing psychological morbidity, with the association being greatest in the youngest age group and least in the oldest subgroup.

Remaining tests for interaction were not statistically significant, indicating that the Gulf War deployment was not more strongly associated with increased psychological morbidity in one subgroup of service type or rank, when compared with other subgroups.

In both study groups, psychological morbidity was greatest in the Army, compared with the Navy and Air Force.

Table 11.7 GHQ-12 cases: The effects of study group across subgroups of age, service type and rank.

	GHQ-12 cases (GHQ-12 ≥ 2)							
	GWV (N=1422)		Comp grp (N=1544)					
	n	(%)†	n	(%)†	Crude OR	Adj OR§	95% CI	P value
All subjects	**564**	**(39.6)**	**502**	**(32.5)**	**1.4**	**1.4**	**1.2-1.6**	**<0.001**
Age								
< 20	74	(42.8)	29	(22.8)	2.5	2.6	1.5-4.3	
20-24	164	(40.6)	123	(31.3)	1.5	1.5	1.1-2.0	
25-34	267	(39.7)	266	(34.1)	1.3	1.3	1.0-1.6	0.040‡
≥ 35	59	(34.1)	84	(34.4)	1.0	1.1	0.7-1.6	
Service Type								
Navy	488	(39.7)	355	(31.7)	1.4	1.5	1.2-1.7	
Army	41	(47.1)	69	(40.4)	1.3	1.3	0.7-2.1	0.484‡
Air Force	35	(33.3)	78	(30.8)	1.1	1.1	0.7-1.8	
Rank								
Officer	94	(35.1)	117	(30.0)	1.3	1.3	0.9-1.8	
Other rank-supervisory	267	(39.0)	260	(35.2)	1.2	1.2	1.0-1.5	0.065‡
Other rank-non supervisory	202	(43.2)	125	(30.0)	1.8	1.8	1.4-2.4	

† Percentage of subjects within each subgroup of age, service type or rank
§ Odds ratios are adjusted for service type, rank and age (< 20, 20-24, 25 to 34, ≥35 years), education and marital status
‡. P value for interaction

11.4.3 Posttraumatic Stress Disorder Checklist (PCL-S)

1339 (94.0%) Gulf War veterans and 1452 (93.7%) comparison group subjects completed the PCL-S in the postal questionnaire.

Table 11.8 presents the prevalence of PCL-S cases (PCL-S score ≥ 50) for all Gulf War veteran and comparison group subjects, and for all subjects within subgroups of age, service type and rank. Gulf War veterans were more likely, than comparison group subjects, to be suffering symptoms indicative of posttraumatic stress disorder, as measured by this instrument. This difference between the two study groups was statistically significant within most age and rank categories. The association between Gulf War service and increased psychological morbidity, however, did not differ across subgroups of age, service type or rank.

In both study groups, PCL-S caseness was most common in the Army, compared with the Navy and Air Force. Posttraumatic stress disorder, as assessed using this measure, was also most common in the oldest subjects in both groups, and in the lowest ranks in the Gulf War veteran group.

Table 11.8 PCL-S cases: The effects of study group across subgroups of age, service type and rank.

	PCL-S cases (PCL-S ≥ 50)							
	GWV (N=1339)		Comp grp (N=1452)					
	n	(%)†	n	(%)†	Crude OR	Adj OR§	95% CI	P value
All subjects	**105**	**(7.9)**	**66**	**(4.6)**	**1.8**	**2.0**	**1.5-2.9**	**<0.001**
Age								
< 20	13	(7.9)	3	(2.6)	3.2	3.1*	0.8-17.7	
20-24	31	(8.2)	14	(3.8)	2.2	2.2	1.1-4.3	
25-34	40	(6.4)	28	(3.8)	1.7	1.9	1.2-3.2	0.584‡
≥35	21	(12.5)	21	(9.0)	1.5	1.7	0.9-3.4	
Service Type								
Navy	86	(7.5)	45	(4.3)	1.8	2.1	1.4-3.1	
Army	13	(15.1)	13	(7.9)	2.1	2.2	0.9-5.1	0.930‡
Air Force	6	(6.1)	8	(3.4)	1.9	1.7	0.6-5.2	
Rank								
Officer	9	(3.6)	11	(3.0)	1.2	1.5	0.6-3.7	
Other rank-supervisory	49	(7.6)	37	(5.3)	1.5	1.8	1.1-2.9	0.350‡
Other rank-non supervisory	47	(10.6)	18	(4.7)	2.4	2.9	1.6-5.2	

† Percentage of subjects within each subgroup of age, service type or rank
§ Odds ratios are adjusted for service type, rank and age (< 20, 20-24, 25 to 34, ≥35 years), education and marital status
‡. P value for interaction
* Where numbers are small odds ratios are adjusted for service type, rank and age (<25 vs ≥25 years) only. Confidence intervals for these adjusted odds ratios were obtained using exact methods for stratified 2x2 tables

11.4.4 Alcohol Use Disorders Identification Test (AUDIT)

1421 (99.8%) Gulf War veterans and 1546 (99.9%) comparison group subjects completed the AUDIT in the postal questionnaire.

Table 11.9 presents the prevalence of AUDIT cases (AUDIT score ≥ 8) for all Gulf War veteran and comparison group subjects, and for all subjects within subgroups of age, service type and rank. Gulf War veterans were more likely, than comparison group subjects, to be problem drinkers as measured by this instrument.

The risk of problem drinking, associated with the Gulf War deployment, was greatest for the youngest Gulf War veterans, those in the Navy and those in the lowest ranks. These differences in risk across subgroups of age, service type and rank reached statistical significance.

Table 11.9 AUDIT cases: The effects of study group across subgroups of age, service type and rank

	AUDIT cases (AUDIT ≥ 8)							
	GWV (N=1421)		Comp grp (N=1546)					
	n	(%)†	n	(%)†	Crude OR	Adj OR§	95% CI	P value
All subjects	**517**	**(36.4)**	**464**	**(30.0)**	**1.3**	**1.2**	**1.0-1.4**	**0.014**
Age								
< 20	75	(43.4)	41	(32.5)	1.6	1.7	1.0-2.8	
20-24	166	(41.1)	112	(28.6)	1.7	1.6	1.2-2.2	
25-34	222	(33.1)	231	(29.5)	1.2	1.0	0.8-1.3	0.037‡
≥ 35	54	(31.0)	80	(32.7)	0.9	0.9	0.6-1.4	
Service Type								
Navy	483	(39.6)	374	(33.4)	1.3	1.3	1.1-1.6	
Army	24	(27.6)	49	(28.5)	1.0	0.9	0.5-1.7	0.025‡
Air Force	10	(9.5)	41	(16.2)	0.5	0.5	0.2-1.0	
Rank								
Officer	53	(19.8)	78	(19.9)	1.0	0.8	0.5-1.2	
Other rank-supervisory	254	(37.1)	265	(35.8)	1.0	1.0	0.8-1.3	<0.001‡
Other rank-non supervisory	209	(44.7)	121	(29.2)	2.0	2.0	1.5-2.7	

† Percentage of subjects within each subgroup of age, service type or rank
§ Odds ratios are adjusted for service type, rank and age (< 20, 20-24, 25 to 34, ≥35 years), education and marital status
‡. P value for interaction

The AUDIT total score is derived from subcategories of questions which are representative of hazardous drinking (related to quantity and frequency of drinking), alcohol dependence (drinking behaviour indicative of an addiction) and harmful drinking (consequences of drinking which suggest harm to self or others). When analysed on the basis of these subcategories (data not shown), approximately 80% of the AUDIT score is being derived

from high levels of hazardous drinking in this population, with only low levels of alcohol dependence and harmful drinking evident from responses to this questionnaire.

11.4.5 All Gulf War veterans versus comparison group subjects who had been on active deployments

Approximately one third of the comparison group (N=514) reported that they had been on at least one active, war like deployment. Of these, all 514 completed the AUDIT, 513 completed the GHQ-12, 488 completed the PCL-S and 450 completed the psychologist administered CIDI. The prevalence of CIDI defined psychological disorders present in the previous 12 months, and GHQ-12, PCL-S and AUDIT caseness is shown in Table 11.10 for Gulf War veterans and for those comparison group subjects who had been on an active deployment.

Table 11.10 CIDI disorders present within 12 months and GHQ-12, PCL-S and AUDIT caseness in Gulf War veterans and comparison group subjects who had been on active deployments

	Gulf War veterans		Comparison group				
	n	(%)	n	(%)	Adj OR‡	95% CI	P value
CIDI disorders	**N=1381**		**N=450**				
Any affective disorder	144	(10.4)	28	(6.2)	1.5	1.0-2.4	0.065
Any anxiety disorder	177	(12.8)	37	(8.2)	1.9	1.1-3.1	0.015
Posttraumatic stress disorder	71	(5.1)	11	(2.4)	2.2	1.1-4.6	0.032
Any substance use disorder	67	(4.9)	12	(2.7)	1.6	0.9-3.1	0.140
Any CIDI disorder	284	(20.6)	65	(14.4)	1.4	1.0-2.0	0.030
	N=1422		**N=513**				
GHQ-12 cases	564	(39.6)	185	(36.1)	1.1	0.9-1.4	0.370
	N=1339		**N=488**				
PCL-S cases	105	(7.9)	22	(4.5)	1.9	1.1-3.1	0.015
	N=1421		**N=514**				
AUDIT cases	517	(36.4)	152	(29.6)	1.1	0.9-1.4	0.481

‡ Odds ratios are adjusted for service type, rank and age (< 20, 20-24, 25 to 34, ≥35 years), education, marital status and pre-Gulf War disorders of the same type

When the statistical analysis is restricted to only those comparison group subjects who have been on active deployments, the statistical power of the analysis to detect small differences in psychological health outcomes between the two study groups is reduced. Despite this reduction in statistical power, Table 11.10 shows that when Gulf War veterans are compared with only those comparison group subjects who have been on active deployments, risk of CIDI disorders in the previous twelve months and risk of PCL-S caseness remains heightened in the Gulf War veteran group. For most of the measures of recent psychological morbidity shown in Table 11.10, the adjusted odds ratios are only slightly reduced compared with those presented in previous tables where Gulf War veterans were compared with all comparison group subjects. The exception is the adjusted odds ratio for 'any substance disorder' which

actually remains the same. As expected, however, the confidence intervals are slightly wider than those previously presented. The elevated risk of psychological morbidity in Gulf War veterans remains statistically significant for 'any CIDI disorder', 'any anxiety disorder', posttraumatic stress disorder and PCL-S caseness, but the risk is no longer statistically significantly elevated for 'any affective disorder', 'any substance disorder', GHQ-12 caseness and AUDIT caseness, when only those comparison group subjects who have been on active deployments are included in the analysis.

11.4.6 Gulf War veteran group subanalysis: the effects of Gulf War-related exposures on psychological disorders in Gulf War veterans

For Gulf War veterans, Table 11.11 through to Table 11.17 present the effects of Gulf War service related Military Service Experience (MSE) questionnaire scores, total number of immunisations and deployment era (deployment completed before or after the commencement of the air war on 17 January 1991) upon CIDI defined post-Gulf War psychological disorders and GHQ-12, PCL-S and AUDIT caseness. These analyses are confined to Gulf War veterans only.

Increasing number of psychological stressors, as indicated by increasing score on the MSE questionnaire, was strongly associated with increasing risk for all psychological disorder measures. Differences in odds ratios across MSE score categories were statistically significant after adjustment for service type, rank, age, education and marital status. The statistically significant dose response slopes indicate that the expected increase in the odds of any disorder, per unit increase in MSE score, varied from 7% for the AUDIT measure to more than 20% for the two measures of posttraumatic stress disorder.

The effect of total number of immunisations upon risk of psychological disorders was mixed. Compared with Gulf War veterans who reported no immunisations, those who reported a small number of immunisations typically had better psychological health, while those who reported large numbers of immunisations typically had similar or poorer psychological health. Gulf War veterans who did not know how many immunisations they received, were also likely to have similar or poorer psychological health than those who reported no immunisations. Amongst Gulf War veterans who reported any immunisations, and for most measures of psychological health with the exception of the AUDIT, statistically significant dose response slopes indicated that the odds of psychological morbidity increased with every unit increase in number of reported immunisations. The dose response slope was steepest for the CIDI measures of any anxiety and posttraumatic stress disorder and for the PCL.

PCL-caseness was statistically significantly more prevalent amongst Gulf War veterans whose deployments continued after the air war commenced on 17 January 1991, than amongst Gulf War veterans who had completed their deployments by this time. Post-Gulf War posttraumatic stress disorder was also higher in the Gulf War veterans whose deployments continued after the air war, however this difference did not reach statistical significance. There were no other notable differences in psychological health outcomes as a function of deployment era.

Table 11.11 Gulf War veterans with any post-Gulf War affective disorder

Gulf War exposure		n	(%)	Crude OR	Adj OR†	95% CI	P value§
MSE questionnaire score							
0 – 4	(N=320)	33	(11)	1.0	1.0	-	
5 – 8	(N=415)	41	(10)	0.9	0.9	0.6-1.5	
9 – 12	(N=316)	55	(18)	1.9	1.9	1.2-3.0	<0.001
> 12	(N=369)	120	(35)	4.5	4.5	2.9-7.1	
Dose response slope‡		-	-	1.13	1.14	1.11-1.17	<0.001
Immunisations							
None	(N=115)	24	(21)	1.0	1.0	-	-
Any	(N=907)	157	(17)	0.8	0.7	0.4-1.1	0.124
1 – 4	(N=251)	29	(12)	0.5	0.4	0.2-0.8	
5 – 9	(N=533)	102	(19)	0.9	0.8	0.5-1.3	
≥ 10	(N=123)	26	(21)	1.0	0.8	0.4-1.6	
Don't know	(N=318)	67	(21)	1.0	0.8	0.5-1.4	0.409
Dose response slope‡		-	-	1.06	1.05	1.00-1.11	0.059
Deployment completed before the air war							
Yes	(N=315)	51	(16)	1.0	1.0	-	-
No	(N=1028)	199	(19)	1.2	1.1	0.8-1.5	0.642

†. Odds ratios are adjusted for service type, rank and age (< 20, 20-24, 25 to 34, ≥35 years), education and marital status
‡. Dose response slope is the expected proportionate increase in the odds ratio per unit increase in the MSE questionnaire score or per unit increase in the number of immunisations amongst those who reported 'any' immunisations
§ With the exception of the P values for the dose response slopes, remaining P values assess whether any odds ratios within each exposure variable differ from unity

Table 11.12 Gulf War veterans with any post-Gulf War anxiety disorder

Gulf War exposure		n	(%)	Crude OR	Adj OR†	95% CI	P value§
MSE questionnaire score							
0 – 4	(N=320)	6	(2)	1.0	1.0	-	
5 – 8	(N=415)	11	(3)	1.4	1.3	0.5-3.6	
9 – 12	(N=316)	20	(7)	3.6	3.6	1.4-9.2	<0.001
> 12	(N=369)	67	(21)	12.7	13.0	5.4-31.3	
Dose response slope‡		-	-	1.19	1.19	1.15-1.24	<0.001
Immunisations							
None	(N=107)	7	(7)	1.0	1.0	-	-
Any	(N=805)	68	(8)	1.2	1.1	0.5-2.5	0.850
1 – 4	(N=244)	12	(5)	0.7	0.7	0.3-1.9	
5 – 9	(N=508)	41	(8)	1.3	1.1	0.5-2.6	
≥ 10	(N=113)	15	(13)	2.2	2.0	0.7-5.2	
Don't know	(N=298)	29	(10)	1.6	1.4	0.6-3.3	0.467
Dose response slope‡		-	-	1.12	1.12	1.04-1.20	0.004
Deployment completed before the air war							
Yes	(N=299)	20	(7)	1.0	1.0	-	-
No	(N=968)	85	(9)	1.3	1.2	0.7-2.0	0.481

†. Odds ratios are adjusted for service type, rank and age (< 20, 20-24, 25 to 34, ≥35 years), education and marital status
‡. Dose response slope is the expected proportionate increase in the odds ratio per unit increase in the MSE questionnaire score or per unit increase in the number of immunisations amongst those who reported 'any' immunisations
§ With the exception of the P values for the dose response slopes, remaining P values assess whether any odds ratios within each exposure variable differ from unity.

Table 11.13 Gulf War veterans with any post-Gulf War posttraumatic stress disorder

Gulf War exposure		n	(%)	Crude OR	Adj OR†	95% CI	P value§
MSE questionnaire score							
0 – 4	(N=320)	4	(1)	1.0	1.0*	-	
5 – 8	(N=415)	3	(1)	0.6	0.6*	0.1-3.9	
9 – 12	(N=316)	15	(5)	3.9	4.2*	1.3-18.3	<0.001
> 12	(N=369)	50	(14)	12.2	14.4*	4.9-57.9	
Dose response slope‡		-	-	1.21	1.23	1.17-1.28	<0.001
Immunisations							
None	(N=116)	6	(5)	1.0	1.0	-	-
Any	(N=916)	37	(4)	0.8	0.8	0.3-2.0	0.611
1 – 4	(N=256)	4	(2)	0.3	0.3	0.1-1.2	
5 – 9	(N=538)	23	(4)	0.8	0.8	0.3-2.1	
≥10	(N=122)	10	(8)	1.6	1.9	0.6-5.6	
Don't know	(N=327)	29	(9)	1.8	1.9	0.7-4.9	0.181
Dose response slope‡		-	-	1.17	1.18	1.08-1.30	<0.001
Deployment completed before the air war							
Yes	(N=318)	10	(3)	1.0	1.0	-	-
No	(N=1044)	63	(6)	2.0	1.8	0.9-3.6	0.100

†. Odds ratios are adjusted for service type, rank and age (< 20, 20-24, 25 to 34, ≥35 years), education and marital status

‡. Dose response slope is the expected proportionate increase in the odds ratio per unit increase in the MSE questionnaire score or per unit increase in the number of immunisations amongst those who reported 'any' immunisations

§ With the exception of the P values for the dose response slopes, remaining P values assess whether any odds ratios within each exposure variable differ from unity.

* These odds ratios are adjusted for service type, rank and age (<25 vs ≥25 years) only. CI values for these adjusted odds ratios were obtained using exact methods for stratified 2x2 tables

Table 11.14 Gulf War veterans with any post-Gulf War substance use disorder

Gulf War veterans with any post-Gulf War substance use disorder							
Gulf War exposure		**n**	**(%)**	**Crude OR**	**Adj OR†**	**95% CI**	**P value§**
MSE questionnaire score							
0 – 4	(N=320)	26	(11)	1.0	1.0	-	
5 – 8	(N=415)	41	(14)	1.4	1.2	0.7-2.0	
9 – 12	(N=316)	51	(22)	2.4	2.3	1.3-3.9	<0.001
> 12	(N=369)	95	(35)	4.4	3.8	2.3-6.4	
Dose response slope‡		-	-	1.10	1.10	1.07-1.13	<0.001
Immunisations							
None	(N=89)	17	(19)	1.0	1.0	-	-
Any	(N=699)	126	(18)	0.9	0.7	0.4-1.3	0.213
1 – 4	(N=196)	26	(13)	0.6	0.5	0.2-1.0	
5 – 9	(N=409)	72	(18)	0.9	0.7	0.3-1.3	
≥10	(N=94)	28	(30)	1.8	1.2	0.5-2.5	
Don't know	(N=241)	69	(29)	1.7	0.9	0.5-1.8	0.812
Dose response slope‡		-	-	1.09	1.07	1.00-1.13	0.047
Deployment completed before the air war							
Yes	(N=245)	47	(19)	1.0	1.0	-	-
No	(N=785)	167	(21)	1.1	1.1	0.7-1.6	0.623

†. Odds ratios are adjusted for service type, rank and age (< 20, 20-24, 25 to 34, ≥35 years), education and marital status
‡. Dose response slope is the expected proportionate increase in the odds ratio per unit increase in the MSE questionnaire score or per unit increase in the number of immunisations amongst those who reported 'any' immunisations
§ With the exception of the P values for the dose response slopes, remaining P values assess whether any odds ratios within each exposure variable differ from unity.

Table 11.15 Gulf War veterans with GHQ-12 score ≥ 2

Gulf War exposure		n	(%)	Crude OR	Adj OR†	95% CI	P value§
MSE questionnaire score							
0 – 4	(N=320)	66	(21)	1.0	1.0	-	
5 – 8	(N=415)	128	(31)	1.7	1.7	1.2-2.5	
9 – 12	(N=316)	144	(46)	3.2	3.2	2.3-4.7	<0.001
> 12	(N=369)	226	(61)	6.1	6.1	4.2-8.7	
Dose response slope‡		-	-	1.13	1.13	1.11-1.16	<0.001
Immunisations							
None	(N=119)	46	(39)	1.0	1.0	-	-
Any	(N=956)	375	(39)	1.0	0.9	0.6-1.4	0.723
1 – 4	(N=267)	90	(34)	0.8	0.7	0.5-1.2	
5 – 9	(N=563)	214	(38)	1.0	0.9	0.6-1.4	
≥ 10	(N=126)	71	(56)	2.0	1.8	1.1-3.1	
Don't know	(N=342)	141	(41)	1.1	1.0	0.6-1.5	0.827
Dose response slope‡		-	-	1.09	1.09	1.04-1.14	<0.001
Deployment completed before the air war							
Yes	(N=331)	117	(35)	1.0	1.0	-	-
No	(N=1090)	446	(41)	1.3	1.2	0.4-1.5	0.231

†. Odds ratios are adjusted for service type, rank and age (< 20, 20-24, 25 to 34, ≥35 years), education and marital status
‡. Dose response slope is the expected proportionate increase in the odds ratio per unit increase in the MSE questionnaire score or per unit increase in the number of immunisations amongst those who reported 'any' immunisations
§ With the exception of the P values for the dose response slopes, remaining P values assess whether any odds ratios within each exposure variable differ from unity.

Table 11.16 Gulf War veterans with PCL-S score ≥ 50

Gulf War exposure		n	(%)	Crude OR	Adj OR†	95% CI	P value§
MSE questionnaire score							
0 – 4	(N=320)	5	(2)	1.0	1.0*	-	
5 – 8	(N=415)	12	(3)	1.9	2.0*	0.6-7.3	
9 – 12	(N=316)	21	(7)	4.4	4.2*	1.5-14.7	<0.001
> 12	(N=369)	67	(19)	13.4	13.8*	5.3-45.7	
Dose response slope‡		-	-	1.20	1.22	1.17-1.27	<0.001
Immunisations							
None	(N=116)	10	(9)	1.0	1.0	-	-
Any	(N=894)	56	(6)	0.7	0.6	0.3-1.3	0.234
1 – 4	(N=250)	7	(3)	0.3	0.3	0.1-0.8	
5 – 9	(N=526)	36	(7)	0.8	0.7	0.3-1.5	
≥10	(N=118)	13	(11)	1.3	1.3	0.5-3.4	
Don't know	(N=324)	38	(12)	1.4	1.3	0.6-2.8	0.543
Dose response slope‡		-	-	1.12	1.14	1.04-1.23	0.003
Deployment completed before the air war							
Yes	(N=305)	12	(4)	1.0	1.0	-	-
No	(N=1033)	93	(9)	2.4	1.9	1.0-3.7	0.039

†. Odds ratios are adjusted for service type, rank and age (< 20, 20-24, 25 to 34, ≥35 years), education and marital status
‡. Dose response slope is the expected proportionate increase in the odds ratio per unit increase in the MSE questionnaire score or per unit increase in the number of immunisations amongst those who reported 'any' immunisations
§ With the exception of the P values for the dose response slopes, remaining P values assess whether any odds ratios within each exposure variable differ from unity.
* These odds ratios are adjusted for service type, rank and age (<25 vs ≥25 years) only. CI values for these adjusted odds ratios were obtained using exact methods for stratified 2x2 tables

Table 11.17 Gulf War veterans with AUDIT score ≥ 8

Gulf War veterans with AUDIT score ≥ 8							
Gulf War exposure		**n**	**(%)**	**Crude OR**	**Adj OR†**	**95% CI**	**P value§**
MSE questionnaire score							
0 – 4	(N=320)	84	(26)	1.0	1.0	-	
5 – 8	(N=415)	133	(32)	1.3	1.2	0.8-1.7	
9 – 12	(N=316)	117	(37)	1.7	1.5	1.1-2.1	<0.001
> 12	(N=369)	183	(50)	2.8	2.5	1.8-3.5	
Dose response slope‡		-	-	1.07	1.07	1.05-1.09	<0.001
Immunisations							
None	(N=119)	39	(33)	1.0	1.0	-	-
Any	(N=956)	329	(34)	1.1	1.0	0.6-1.5	0.992
1 – 4	(N=267)	95	(36)	1.1	1.1	0.7-1.8	
5 – 9	(N=563)	186	(33)	1.0	0.9	0.6-1.5	
≥10	(N=126)	48	(38)	1.3	1.0	0.6-1.8	
Don't know	(N=341)	146	(43)	1.5	1.2	0.7-1.9	0.493
Dose response slope‡		-	-	1.00	0.98	0.94-1.03	0.419
Deployment completed before the air war							
Yes	(N=330)	109	(33)	1.0	1.0	-	-
No	(N=1090)	407	(37)	1.2	1.2	0.9-1.6	0.128

†. Odds ratios are adjusted for service type, rank and age (< 20, 20-24, 25 to 34, ≥35 years), education and marital status
‡. Dose response slope is the expected proportionate increase in the odds ratio per unit increase in the MSE questionnaire score or per unit increase in the number of immunisations amongst those who reported 'any' immunisations
§ With the exception of the P values for the dose response slopes, remaining P values assess whether any odds ratios within each exposure variable differ from unity.

11.4.7 Investigation of possible participation bias

In chapter 6 we presented details of an imputation (ie. prediction) method for assessing possible participation bias in the study. In brief, initially SF-12 scores were imputed for non-participants using the full participant and (principally) the telephone respondent data. Subsequently, these imputed values were used to further impute values of health outcomes for the non-participants, producing a "complete" dataset. This procedure, replicated 100 times, was applied to each of the major psychological health outcomes, each time computing an age, rank and service adjusted odds ratio for the relative health of Gulf War veterans versus comparison group subjects. The average of the 100 imputed odds ratios represents the best estimate, based on the observed data and the imputation model for the health status of non-participants, of the true odds ratio underlying the relative health of Gulf War veterans and comparison group subjects. The difference between the average imputed odds ratio and the actual observed odds ratio among participants reflects the degree of participation bias, and is the focus of this assessment.

The results of the 100 imputed datasets are shown in Table 11.18 along with the odds ratios observed for participants, for CIDI-defined post-Gulf War disorders and for GHQ-12, PCL-S and AUDIT caseness.

Table 11.18 Imputed "complete sample" odds ratios and prevalences compared with those of full participants

	Participants			Imputed results			
Psychological health outcome	**GWV prevalence**	**Comp. group prevalence**	**Odds Ratio**	**Average GWV prevalence**	**Average Comp. group prevalence**	**Average Odds Ratio**	**Range**
Post-Gulf War CIDI disorders							
Any affective	18.6%	12.3%	1.60	17.2%	11.8%	1.52	1.32-1.87
Any anxiety	8.3%	3.1%	2.77	7.5%	2.9%	2.68	1.95-3.71
posttraumatic stress disorder	5.4%	1.4%	3.88	4.7%	1.3%	3.78	2.25-5.92
Any substance abuse	20.8%	13.1%	1.51	19.0%	12.8%	1.46	1.18-1.76
GHQ-12 case	39.6%	32.5%	1.38	36.9%	30.9%	1.31	1.18-1.47
PCL-S case	7.9%	4.6%	1.88	6.5%	3.5%	2.00	1.66-2.44
AUDIT case	36.4%	30.0%	1.21	34.9%	28.7%	1.22	1.12-1.37

The average imputed "complete sample" odds ratios were very similar to those observed for full participants. This suggests that the increased risks of psychological disorders, which were observed in participating Gulf War veterans compared with participating comparison group subjects, are unlikely to be due to incomplete participation of all sampled subjects. If participation bias exists, it appears to be slight and possibly leading to a minor underestimation of the odds ratio for PCL-S caseness, and minor overestimation for other disorders apart from AUDIT caseness. Note that all imputed prevalences are lower than the observed prevalences among participants, owing to the SF-12 results for telephone participants indicating better health status than full participants, and this translating to lower imputed prevalences.

This investigation of participation bias, however, needs to be interpreted with considerable caution. Telephone questionnaire respondents may not be representative of the remaining non-participants. Further, their SF-12 responses and the relationship between those and variables such as study group, age and rank may not be predictive of accurate SF-12 scores in the remaining non-participants. Also, the relationship between participants' SF-12 scores and their psychological health outcomes may not be predictive of psychological health outcomes of non-participants.

Despite the limitations of the prediction models and the assumptions made therein, this investigation suggests that participation bias is unlikely to be a significant factor affecting the results of the psychological health outcomes assessed in this study.

11.5 Discussion

Australian male Gulf War veterans demonstrated considerably greater post-Gulf War and recent psychological morbidity than the male comparison group subjects in this study. This finding was consistent across almost every measure contained in the CIDI, GHQ-12, PCL-S and AUDIT instruments. Specifically, since the time of the Gulf War, Gulf War veterans have had greater risk of affective disorders, anxiety disorders including posttraumatic stress disorder (PTSD), substance-use disorders and signs of problem drinking. The increased risk of psychological morbidity in Gulf War veterans persisted after adjustment for age, service type, rank, marital status, education level and pre-Gulf War disorders. Typically the risk associated with the Gulf War deployment was not more elevated in any one subgroup of age, service type or rank. The risk associated with the Gulf War deployment was reduced when Gulf War veterans were compared with those comparison group participants who had been on active deployments. Within Gulf War veterans, there was a strong association between increased reporting of Gulf War related stressful experiences and increasing psychological morbidity on all measures. Mean number of immunisations received and deployment era had no clear effects upon psychological health outcomes.

CIDI defined disorders present within the previous 12 months, were found in approximately 20% of Gulf War veterans and 14% of comparison group subjects. In previous surveys of Gulf War veterans, prevalences of mental disorders have ranged from 15% to 35% of Gulf War veterans.[368] These surveys have typically used self-referred populations and ICD-9 or ICD-10 criteria which have been shown in Australian samples to give slightly higher prevalences of psychological disorder than DSM-IV.[309] In comparison with Australian males aged 35-44 years, who were assessed using the CIDI in the 1997 Australian National Survey of Mental Health and Wellbeing of Adults (NSMHWBA), Gulf War veterans were more likely to have a CIDI defined psychological disorder present within the previous 12 months, and comparison group subjects were less likely.[260, 309] Specifically, Gulf War veterans demonstrated higher recent prevalences for ‘any affective disorder’, ‘any anxiety disorder’, PTSD, obsessive compulsive disorder and social phobia, whereas recent prevalences in the comparison group subjects were very similar to, or lower than, the Australian Survey data for similarly aged males. Both Gulf War veterans and comparison group subjects had lower prevalences for ‘any substance-use disorder’ including alcohol use disorder in the previous 12 months, than the NSMHWBA male sample. The NSMHWBA report did not include data on somatic disorders.

The most prevalent CIDI defined post-Gulf War diagnoses, in both groups, were those in relation to alcohol related disorders. The second and third most prevalent post-Gulf War disorders were major depressive disorders and PTSD. Typically, the most common psychological disorders reported in the international literature for Gulf War veterans are depressive, anxiety and PTSD disorders.[19, 21, 22] The Iowa study, however, reported symptoms of alcohol abuse as more prevalent than types of depression, symptoms of cognitive dysfunction and symptoms of anxiety including PTSD.[16]

In the current study Gulf War veterans, relative to the comparison group, were at greatest risk of elevated levels of anxiety disorders including PTSD. The increase in risk for PTSD was four-fold using the CIDI diagnoses and two-fold using the PCL. Post-Gulf War anxiety

disorders, including PTSD, were most common amongst the lowest ranks in both study groups. Within the Gulf War veteran group, increasing numbers of reported Gulf War related stressful experiences were strongly associated with increased levels of post-Gulf War anxiety disorders including PTSD. The risk of PTSD was greatest amongst Gulf War veterans who were still in the Gulf region at the time of the air war in January 1991. Amongst Gulf War veterans who reported any immunisations, the odds of PTSD increased with increasing number of immunisations received, however,

The King's College study[155] and the Canadian study of (primarily) Naval Gulf War veterans,[22] both found three-fold increases in their measures of PTSD in Gulf War veterans compared with comparison groups. The increase in PTSD, reported in the Iowa study of Gulf War veterans, was two-fold.[16] Within Gulf War veterans, King's College reported a trend of increasing PTSD with decreasing rank whilst the Canadian study found no association with rank. The US Persian Gulf Veterans' Coordinating Board found increased complaints among Reservists, but no association with other war exposure or demographic factors. Consistent with our finding of an association between anxiety disorders and increased reporting of Gulf War related stressful experiences, Sutker *et al* reported higher war-zone exposures in veterans with PTSD and the Canadian study[22] found more symptoms of PTSD in Gulf War veterans with additional war theatre experience. King's College reported no association between PTSD and service type, but strong associations with war related psychological stressors such as seeing maimed soldiers and dismembered bodies, dealing with prisoners of war, and the sounding of chemical alarms.[21]

The percentages of subjects currently with PTSD, as measured by the PCL, was notably higher than the percentages diagnosed as having recent PTSD using the psychologist administered CIDI interview. The magnitude of this difference is larger than expected considering that the PCL-S was designed to directly reflect the diagnostic criteria for PTSD as outlined in DSM-IV, just as the CIDI was similarly designed. In their study of Australian veterans of the Vietnam War, Forbes *et al* found that veterans self-rated their PTSD symptoms, on the PCL, as slightly more severe than the clinician ratings.[366] In our study the differences between the self-report measure of the PCL, and the more rigorously applied psychologist administered CIDI, may reflect general over reporting of symptom severity amongst study participants, or genuine differences between the two instruments in their application of the DSM-IV criteria, or differences in their sensitivity and specificity for detecting true cases of PTSD. For example, the use of a PCL-S symptom score of ≥ 50 as the cut-off score for predicting cases of PTSD, may be too low for this population.

It was not uncommon for study participants with anxiety disorders to have more than one diagnosis of this kind. Comorbidity across anxiety disorders, and with PTSD, may partly account for the increased prevalences of CIDI defined obsessive compulsive disorder, generalised anxiety disorder, social phobia and panic disorder and/or agoraphobia in Gulf War veterans. With the exception of generalised anxiety disorder, similar increases in Gulf War veterans have not been reported in previous literature. Comorbidity across psychological disorders, however, is not uncommon. Analysis of the NSMHWBA data showed that 63% of Australian men with PTSD met criteria for at least two other psychiatric disorders. [369]

The increased risk of CIDI defined post-Gulf War substance use disorders, in Gulf War veterans, was one and a half times that in the comparison group. These disorders were primarily alcohol related and most common in the youngest participants, in the Navy service and in the lowest ranks in both study groups. The Gulf War deployment was also associated

with greatest risk in these subgroups when problem drinking was assessed using the AUDIT. Within the Gulf War veteran group, increasing numbers of reported Gulf War related stressful military service experiences were strongly associated with increased levels of post-Gulf War substance use disorders and current problem drinking, however presence in the Gulf region during and after the first air war was not associated. Increasing numbers of immunisations, amongst Gulf War veterans who reported any immunisations, was weakly associated with increased levels of post-Gulf War CIDI defined substance use disorders but not with the AUDIT measure of problem drinking.

The general pattern of increasing substance use disorder with decreasing age is a common pattern shown in the NSMHWBA data for men.[260] The overall levels of CIDI defined alcohol disorders, however, were lower in study participants than those reported for the Australian male population.[260] The AUDIT predicted higher levels of problem drinking in the two study groups, but much of the total AUDIT score in study participants was derived from high quantities of alcohol consumption rather than patterns of drinking suggestive of addictive or harmful behaviour. For some subjects, such hazardous drinking levels may be precursors to later alcohol dependence or abuse and the associated health effects of these alcohol disorders. The risk of these is greater in the Gulf War veteran group where the total AUDIT scores were higher.

Few previous studies have reported alcohol disorders in Gulf War veterans. Of those that have reported on these disorders, the Iowa study found increased symptoms of alcohol abuse in Gulf War veterans and an association with National Guard or Reservist service. The Canadian study[22] in contrast, found no difference between Gulf War veterans and a comparison group on their measure of 'alcohol abuse'. Within Gulf War veteran groups, Dlugosz *et al*[217] reported increased alcohol related disorders in men who served in ground war combat occupations and Ismail *et al*[370] reported increased alcohol related disorders in disabled Gulf War veterans.

Affective disorders were primarily disorders of major depressive type and the increased risk in the Gulf War veteran group was one and a half times that of the comparison group. In both study groups, post-Gulf War affective disorders were most prevalent in the younger age groups, in the Army and in the lower ranks. The risk associated with Gulf War service, however, did not differ across the subgroups of age, service type and rank. Within the Gulf War veteran group affective disorders were strongly associated with increasing numbers of Gulf War related stressful military service experiences. There was no clear association with reported immunisations or with deployment era.

The Iowa study found a two-fold increase in major depression and the Canadian study found a four-fold increase in symptoms of depression, in their Gulf War veteran groups compared with non-Gulf comparison groups. The Iowa group reported associations with chemical and environmental contaminants and the Canadian group reported greatest risk amongst lowest ranks.

Despite previous studies which have recorded somatic symptoms or somatic disorders in Gulf War veterans[14, 19] the least prevalent diagnoses in both study groups in our study were those in relation to somatic disorders. These were diagnosed in less than one percent of all subjects and somatisation disorder, in particular, was not diagnosed in any participants. This suggests that Australian Gulf War veterans do not seem to be reporting unexplained, recurrent and multiple symptoms at sufficiently high levels to meet DSM-IV criteria for a somatisation disorder.

Subjects in the lowest subgroup of rank typically recorded the highest levels of psychological morbidity in both study groups. Risk in this subgroup of Gulf War veterans, however, was no greater than that for the lowest ranks in the comparison group. It has been suggested that rank could be a proxy for socioeconomic status, which is associated with both psychological and physical morbidity in civilian populations.[155] For most measures of psychological morbidity in our study however, the association with rank persisted after adjustment for several demographic and socioeconomic variables such as age, marital status and education. It is possible that rank could be associated with levels of training, combat experience and soldier quality, which McDuff *et al*[178] listed as important predictors of stress-related casualties. The category 'other ranks – nonsupervisory' includes the very newest ADF recruits who have completed basic training. Personnel categorised as 'Other ranks-supervisory' are more experienced, having achieved a minimum of two years service experience before becoming eligible for promotion to the lowest supervisory rank (Leading Seaman in the Navy, and Corporal in the Army and Airforce). Officers receive more formal military education than other ranks, however, whilst this group includes the most highly ranked and experienced of the ADF personnel, it also includes newly recruited and trained officers with little or no "on-the-job" experience.

It does not appear that the increased risk of psychological disorders in Gulf War veterans can be explained as a 'deployment effect', whereby military personnel who deploy to any active, warlike environment may subsequently be found to have poorer psychological health than military personnel who have not been actively deployed. We compared the Gulf War veterans with the comparison group subjects who had also been on active deployments and found the increased risk of psychological disorders in Gulf War veterans to be only slightly reduced. The reduced statistical power of this analysis, however, contributed toward a widening of the confidence intervals and measures of affective and substance use disorders in the previous twelve months, problem drinking using the AUDIT and GHQ-12 caseness were no longer statistically significantly higher. CIDI measures of 'any anxiety disorder' and posttraumatic stress disorder in the previous twelve months, did, however remain statistically significantly elevated in the Gulf War veteran group when they were compared with actively deployed comparison group subjects. Interpretation of this finding is limited by the fact that the numbers of comparison group subjects reporting active deployments were relatively small and the destination and nature of these deployments were many and varied. The results, however, suggest that whilst a deployment effect may partially explain the difference in psychological health risk between the two groups, it by no means fully explains the elevated risk in the Gulf War group.

Gulf War related stressful military service experiences were more frequently reported by Gulf War veterans with psychological disorders than by Gulf War veterans without psychological disorders. This finding was consistent across all measures of psychological morbidity in our study. In chapter 8 it was shown that stressful military service experiences relevant to the Gulf War were usually related to perceived threat of attack, fear for one's safety, threat of chemical or biological warfare attack, a sense of lack of control and uncomfortable environmental conditions. These were most frequently reported by the youngest age groups, by the Army service and by the lowest ranks; the same groups most associated with increased psychological ill-health in our study. Therefore, it is possible that the trends for poorer psychological health to be amongst those who are lower in rank, younger and in the Army service, are related to higher exposure to stressful military service experiences in these groups.

The link between traumatic or stressful exposure and subsequent psychopathology needs to be interpreted cautiously. Some prospective studies of Gulf War veterans,[371] and veterans of the 1994 conflict in Somalia,[283] have demonstrated that as PTSD symptoms increase, so does amplification of memory for traumatic or stressful events. These findings raise questions about the validity of any retrospectively determined relationship between the level of exposure to trauma and degree of PTSD symptoms. Such recall bias can not be ruled out in our study where those Australian Gulf War veterans who have had poor psychological health may experience heightened recall of levels of fear and threat.

There was no clear effect of Gulf War immunisation exposure upon psychological health outcomes in Gulf War veterans. Small numbers of immunisations appeared to be slightly protective against psychological morbidity, with poorer psychological health in Gulf War veterans who received no immunisations, in those who received many immunisations and in those who did not know how many immunisations they had received. Within those Gulf War veterans who reported some immunisations, there was increasing psychological morbidity with increasing numbers of immunisations. Findings in the international literature have also been mixed. Hotopf *et al*[61] found that multiple immunisations received before deployment were associated with symptoms of PTSD, but immunisations received during deployment were not associated with this health outcome. Unwin *et al*[21] found that the receipt of immunisations against agents of biological warfare (plague and anthrax with pertussis adjuvant) was associated with a slightly increased risk of a multisymptom illness in the Gulf War veteran group, but those who received routine immunisations were generally not at increased risk.

Unwin *et al*[21] reported further analysis which suggested that the association between administration of immunisations and illness may have been attributable to a biased recollection of immunisation side effects and later illness. If similar recall bias was systematically occurring amongst Australian Gulf War veterans with poor psychological health, it would be likely that we would see a consistent dose response relationship between increasing numbers of immunisations and increasing psychological morbidity. This pattern is observed amongst Australian Gulf War veterans who report receiving some immunisations. However, this pattern is not repeated when Gulf War veterans who report no immunisations are compared with those who report some immunisations. Therefore, whilst some over reporting of immunisations may be occurring amongst Gulf War veterans with psychological disorders, this does not appear to be occurring systematically throughout the study group.

Posttraumatic stress disorder was more prevalent amongst Gulf War veterans whose deployments continued after the commencement of the air war in January 1991, than amongst Gulf War veterans who had completed their deployments by this time. There were no associations, however, between deployment era and other measures of psychological health. These findings suggest that the exposures or stressors which may have been unique to the air war or the period following, may have contributed to increased risk of posttraumatic stress disorders but are unlikely to have contributed substantially to increased risk of other psychological disorders.

The analysis for the effects of participation bias on psychological health outcomes suggest that our findings are likely to be robust despite some non-participation amongst the comparison group and amongst younger subjects. Whilst there are some limitations to the prediction models and assumptions made therein (see Recruitment chapter for details), the similarity between the observed odds ratios and the summary average imputed odds ratios

provides some reassurance that participation bias is unlikely to be a significant factor effecting the investigation of psychological health in this study.

Having clearly demonstrated elevated risks of several types of psychological disorders in the Gulf War veterans, some additional analyses would be useful to further investigate the pattern of these psychological disorders, possible causes and any associations with physical health outcomes. Analyses could be conducted, for example, to examine the pattern of increasing psychological morbidity in Gulf War veterans across time since the period of the Gulf War. With some limitations associated with the retrospective assessment of health, CIDI data could be used to roughly estimate the time period, after the Gulf War, in which most new disorders first occurred and the average time period for which they persisted. Such information could be useful in identifying the period of time during which veterans are most vulnerable to psychological distress after deployment to war.

Increased reporting of physical health symptoms has been shown for Australian Gulf War veterans in our report (see Chapter 9), and is commonly found in Gulf War veteran populations, with no adequate explanation. Several previous studies have shown that physical symptom reporting is increased in veterans and civilian populations with psychological disorders.[260, 372, 373] Additional analyses in our study would be useful to investigate whether the increased levels of psychological disorder in our Gulf War veterans can partially explain the increased reporting of physical symptoms.

Few causal explanations have been provided in previous studies for the increase in psychological disorders in Gulf War veterans. Further analyses in our study would be useful to identify those subgroups of Gulf War veterans at greatest risk of these disorders. In addition to finding an association between psychological disorders and increased reporting of stressful military experiences in general, additional analyses could determine whether particular types of stressful experiences are more highly associated with psychological disorders than others. Whilst there were mixed associations between psychological disorders and deployment era and immunisations, other characteristics of the Gulf War deployment which differ between veterans remain to be investigated. Different Operations, ships, units and squadrons, primary duties and levels of exposures to chemical and environmental agents may be differentially associated with the elevated risk of psychological distress in Gulf War veterans.

Our study has a number of strengths over previous studies investigating psychological health in Gulf War veteran populations. In contrast to many previous studies, our investigation of psychological health included a very large proportion of the Australian Gulf War veteran population, and a similar sized comparison group who did not deploy to the Gulf War. We also used structured psychological interviews administered by trained, clinical psychologists in addition to the administration of several validated self-report psychological health instruments. Our study results, however, are consistent with previous findings. After rigorous psychological assessment, Gulf War veterans clearly demonstrate increased risks of affective disorders, anxiety disorders including PTSD and substance and alcohol disorders. The greatest risk is for elevated anxiety disorders. The fact that these risks are elevated more than a decade following the Gulf War suggests a high level of chronicity and possibly poor prognosis. The implications for the Department of Veterans' Affairs, in terms of health care costs and disability payments, may be considerable. More important are the costs in terms of human suffering, highlighting the need to ensure access to effective mental health care for this veteran population.

11.5.1 Summary of findings

In summary, and in answer to the research questions posed at the start of this chapter:

Gulf War veterans are considerably more likely, than the comparison group, to have developed a psychological disorder in the period following the Gulf War, and to have had such a disorder present in the last 12 months. Greatest risk is for elevated levels of anxiety disorders including posttraumatic stress disorder. Affective disorders, substance use disorders and signs of problem drinking are also elevated in the Gulf War group.

The risk of psychological morbidity associated with the Gulf War deployment is not more elevated in any one subgroup of age, service type or rank. In both study groups, however, anxiety disorders tend to be highest in the lowest ranks and Army service, alcohol disorders tend to be higher in the youngest participants, lowest ranks and Navy service, and affective disorders tend to be highest in the youngest participants, lowest ranks and Army service.

The increased risk of psychological disorders in Gulf War veterans is only slightly reduced when Gulf War veterans are compared with those comparison group subjects who have also been on an active, warlike deployment. This suggests that a deployment effect may partially, but not fully, explain the increased risk of psychological ill-health in the Gulf War veteran group.

Within the Gulf War veteran group there is a strong association between increased reporting of stressful military experiences during the Gulf War and increasing psychological morbidity. These findings should be interpreted with caution as some studies have demonstrated recall bias in war veterans who are experiencing anxiety symptoms.

There is no clear effect of Gulf War immunisation exposure upon psychological health. Amongst Gulf War veterans who report some immunisations, psychological morbidity increases with increasing numbers of immunisations reported. However, psychological morbidity is typically also heightened amongst Gulf War veterans who report no immunisations and amongst those who report not knowing how many they received.

Posttraumatic stress disorder is heightened in Gulf War veterans whose deployments continued after the commencement of the air war and this may reflect experiences and exposures unique to this deployment era. There is no association, however, between deployment era and other measures of psychological health.

Whilst some limitations must be applied to the interpretation of our investigation of participation bias, the results suggest that non-participation is unlikely to be a major factor explaining the increased risk of psychological disorders in Gulf War veterans in this study.

12. Respiratory health

12.1 Aims

The aim of this analysis is to investigate whether male Australian Defence Force personnel who served in the Gulf War have a higher than expected rate of adverse respiratory health outcomes; and, if so, are these effects associated with exposures and experiences that occurred in the Gulf?

12.2 Research questions

1. Do Australian Gulf War veterans have more respiratory symptoms than the comparison group?
2. Do Australian Gulf War veterans have more respiratory conditions than the comparison group?
3. Do Australian Gulf War veterans have poorer lung function than the comparison group?
4. Do Gulf War veterans who were exposed to smoke and oil from burning oil wells (SMOIL) or to dust storms, or who did not complete their deployment prior to the commencement of the air war, have more respiratory conditions than the comparison group?
5. Do Gulf War veterans who were exposed to SMOIL or dust storms, or who did not complete their deployment prior to the commencement of the air war, have poorer lung function than the comparison group?

12.3 Definitions of respiratory health outcomes

These analyses were based on a number of respiratory health measures such as respiratory symptoms and conditions, current use of asthma medication, and lung function testing using spirometry. These respiratory health measures were also used in combination to further define respiratory conditions such as asthma, chronic bronchitis and emphysema. The following abbreviations are used in this chapter:

- FVC, L = Forced vital capacity, which is a measure of the maximum volume of air which can be exhaled during a forced manoeuvre.
- FEV_1, L = Forced expiratory volume in 1 second is the volume expired in the first second of maximal expiration after a maximal inspiration, which is a measure of how quickly the lungs can be emptied.
- FEV_1/FVC, % = the ratio of Forced Expiratory Volume in 1 second to Forced Vital Capacity expressed as a percentage, which is an index of airflow limitation.
- PEFR, L/sec = Peak expiratory flow rate, which is the maximal expiratory flow rate achieved and occurs early in the FVC. It is an indicator of large airways calibre, or respiratory muscle strength.
- $FEF_{25-75\%}$ = Forced expiratory flow during the middle half (25-75%) of the FVC manoeuvre. This is a sensitive measure of small airways narrowing, which in practice may be seen as subclinical disease before large airways disease.
- $FEF_{75\%}$ = Forced expiratory flow rate at 75% of vital capacity. The interpretation is similar to that of $FEF_{25-75\%}$.

12.3.1 Respiratory symptom definitions

The specific respiratory symptoms used in these analyses were those reported in the Respiratory Health Questionnaire that was administered by a HSA nurse during the medical assessment. They are not the symptoms that were self-reported in the postal questionnaire. The Respiratory Health Questionnaire was based on the European Community Respiratory Health Survey (ECRHS)[303] and the American Thoracic Society questionnaire.[304]

12.3.2 Respiratory condition definitions

The following working definitions of asthma, chronic bronchitis and emphysema were used to compare respiratory conditions between study groups.

Asthma was defined in several ways:

- as self-reported asthma ever.
- as doctor-diagnosed asthma ever.
- as current use of asthma medication, including short- or long-acting beta2-agonists, inhaled corticosteroids, combination inhalers or other respiratory medications.
- according to the ECRHS definition suggestive of asthma[303] as an attack of asthma, or being woken by an attack of shortness of breath, at any time in the last 12 months or current use of asthma medication.

Airflow limitation was defined according to a physiological definition as:

- the ratio of FEV_1/VC <70%[374]

Chronic bronchitis was defined as:

- doctor-diagnosed chronic bronchitis ever.[304, 375]
- chronic obstructive bronchitis, defined as morning, day or night time cough for as much as 3 months in each of the past 2 years and FEV_1/VC < 70%.

Emphysema was defined:

- as doctor-diagnosed emphysema ever.[304]
- according to a working definition as:
  - doctor diagnosed emphysema ever, or
  - shortness of breath when hurrying on level ground or walking up a slight hill and either shortness of breath walking with other people of your own age or having to stop for breath when walking at your own pace on level ground, or
  - FEV_1/FVC <70%.

12.3.3 Lung function definitions

Spirometry was conducted in accordance with the American Thoracic Society (ATS) recommendations,[298] and further assessed during the data analysis as to whether it met the ATS criteria.

The participant's spirometry data were analysed for all indices if they met the ATS criteria of:

- a back extrapolated volume <0.15L (litres) or <5% of FVC, whichever was greater, and
- a minimum of 3 blows, and
- reproducibility, that was the highest and second highest FEV_1 and FVC agreed to within 0.2L of each other.

The values analysed were the:

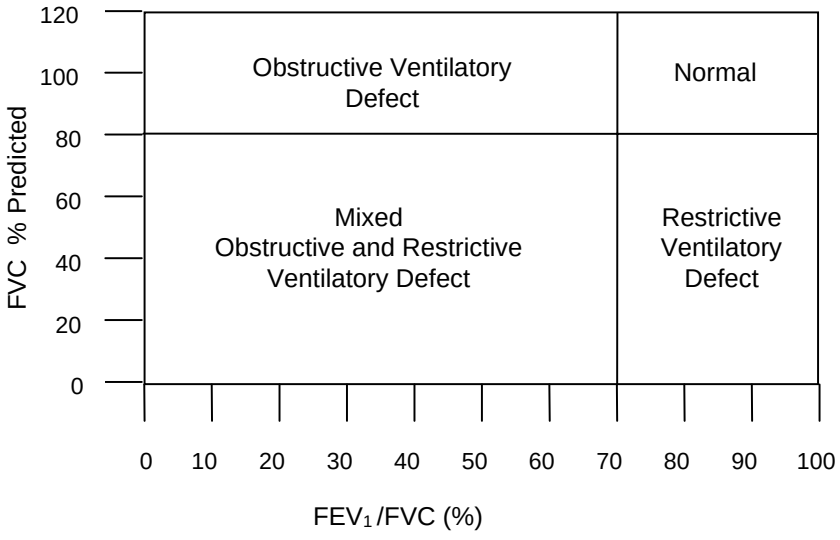
- largest FVC and the largest FEV_1, regardless of whether they come from the same blow,
- $FEV_{1/}FVC$ ratio of the largest FEV_1 and the largest FVC,
- largest peak expiratory flow rate (PEFR),
- forced expiratory flow during the middle half of the FVC manoeuvre ($FEF_{25-75\%}$), and forced expiratory flow rate at 75% of vital capacity ($FEF_{75\%}$) obtained from the single spirogram with the largest sum of FVC plus FEV_1 (ie best test).

Predicted values of lung function indices such as FEV_1 and FVC were calculated using multiple regression equations developed by Knudson *et al*.[376] PEFR was predicted using the multiple regression equation developed by the European Coal & Steel Commission,[377] as regression equations were not developed in the previous[376] study. For each lung function parameter, the multiple regression equation consisted of a constant (the parameter value that would be predicted if the age and height variables were equal to zero), as well as regression coefficients, or weights, for age and height. For example predicted FEV_1 for males ≥25 years of age = –6.5147 +{height (cm) x 0.0665} –{age (years) x 0.0292} (r^2=0.74)

Abnormal ventilatory function in participants was classified according to the following criteria[298, 299] as illustrated in Figure 12.1.

- No abnormality was defined as FVC ≥80% predicted and FEV_1/FVC% ≥ 70%
- Obstructive ventilatory defect was defined as FEV_1/FVC <70% and FVC ≥80%
- Restrictive ventilatory defect was defined as an FVC <80% predicted and FEV_1/FVC % ≥ 70%
- Mixed obstructive and restrictive ventilatory defects were defined as FVC <80% predicted and FEV_1/FVC% <70%

Figure 12.1 Interpretation of spirometry as a function of FVC and FEV_1



12.3.4 Atopy definition

Atopy was defined as a positive response on skin prick testing to one or more allergen extracts (mould mix, house dust mite, grass mix or cat dander). A positive result for an allergen was defined as one in which the response to that allergen (the average mean wheal

diameter) was at least 3mm greater than the average mean wheal diameter of the negative control. The following results were excluded from the analysis:

- Those who indicated that they used antihistamines in the previous 4 days
- A negative positive control, ie. those who did not react to the positive control solution (< 3mm average diameter)
- A positive negative control (≥ 3mm average diameter).

12.4 Gulf War exposure measures

The following exposure metrics were considered in the Gulf War subanalysis, as these were considered most relevant to respiratory health:

- SMOIL exposure (none, any, low, high)
- Dust storm exposure (no, yes)
- Deployment completed before the air war started, ie before 17th January 1991 (yes, no)

As discussed in chapter 8, the SMOIL and dust storm metrics were based on self-reported exposures. The timing of their deployment in relation to the air war was based on data in the Nominal Roll, and was considered to be a more objective measure of their likelihood of exposure to SMOIL, as oil wells were set on fire after the air war had commenced on 17th January 1991.

12.5 Results

12.5.1 Respiratory symptoms

Table 12.1 shows that Gulf War veterans reported all respiratory symptoms more commonly than the comparison group, and they were at higher risk of wheeze, chest tightness, shortness of breath, nocturnal and day or night time cough. Adjustment for potential confounders made little difference to the odds ratios. Gulf War veterans were at greater risk of wheeze according to all definitions - that is, whether they had had wheeze at any time in the last 12 months, and according to more specific definitions of wheeze that was associated with breathlessness or that had occurred when they did not have a cold. Gulf War veterans were also at higher risk of nocturnal chest tightness and shortness of breath (dyspnoea) than the comparison group. Similarly, Gulf War veterans were at greater risk than the comparison group of shortness of breath regardless of whether this shortness of breath had occurred spontaneously at rest or following strenuous activity, or had woken them at night.

Table 12.1 Prevalence and odds ratios (ORs) of respiratory symptoms in the past 12 months

Respiratory symptoms	GWV n (%)	Comp grp n (%)	Crude OR	Adj OR†	95% CI	P value
Wheeze only	345 (24.9)	259 (18.8)	1.4	1.4	1.2-1.7	<0.001
Wheeze when no cold	228 (16.6)	152 (11.1)	1.6	1.6	1.3-2.0	<0.001
Wheeze with breathlessness	171 (12.4)	99 (7.2)	1.8	1.8	1.3-2.3	<0.001
Nocturnal chest tightness	191 (13.9)	137 (10.0)	1.5	1.4	1.1-1.9	0.003
Nocturnal cough	337 (24.3)	250 (18.1)	1.5	1.4	1.1-1.7	<0.001
Morning cough*	144 (10.4)	121 (8.8)	1.2	1.2	0.9-1.5	0.257
Day or night time cough*	206 (14.9)	157 (11.4)	1.4	1.3	1.0-1.6	0.032
Morning sputum*	211 (15.3)	172 (12.5)	1.3	1.2	1.0-1.5	0.084
Spontaneous dyspnoea	106 (7.7)	66 (4.8)	1.7	1.6	1.1-2.2	0.008
Post-exertional dyspnoea	297 (21.6)	231 (16.8)	1.4	1.3	1.1-1.6	0.005
Nocturnal dyspnoea	78 (5.6)	51 (3.7)	1.6	1.5	1.0-2.2	0.032

* The defining question relates to whether the person "usually" coughs or produces sputum at this time
† Odds ratios are adjusted for age (linear term), height (linear term), smoking (0, <10, 10-20, >20 pack years), weight, atopy, rank, service, education and marital status.

The risk of respiratory symptoms across subgroups of service type, age and rank were also examined. There was no increase in risk of respiratory symptoms with age. Army subjects reported more wheeze than Navy or RAAF subjects {Navy 1.3 (1.0-1.6), Army 2.9 (1.5-5.7), RAAF 2.1 (1.0-4.2) P=0.040}. Officers were at lower risk of 'morning sputum' than other ranks {Officer 0.5 (0.6-1.0), other ranks-supervisory 1.4 (1.0-1.9), other ranks-non supervisory 1.5 (1.0-2.2), P=0.022}. There were no other differences across service type or rank subgroups for respiratory symptoms.

12.5.2 Respiratory conditions

Gulf War veterans reported more asthma in accordance with the ECRHS definition suggestive of asthma, but there were no differences between the groups based on alternative definitions (Table 12.2). There was no difference between the study groups for chronic bronchitis or emphysema according to the definitions used in our study.

The proportions of the study groups who reported the respiratory conditions varied according to the definition that was used, and this was most noticeable for chronic bronchitis and emphysema. A greater proportion of the study groups had emphysema according to the working definition compared with doctor-diagnosed emphysema. In contrast, a smaller proportion of the study groups had chronic obstructive bronchitis compared with doctor-diagnosed chronic bronchitis. Although the proportions varied in different directions for definitions of chronic bronchitis and emphysema, the direction was the same for both study groups.

There were no differences in the risk of respiratory conditions across subgroups of age, service type, age or rank (data not shown).

Table 12.2 Prevalence and ORs of respiratory conditions

Respiratory condition	GWV n (%)	Comp grp n (%)	Crude OR	Adj OR*	95% CI	P value
Asthma						
Asthma ever	190 (13.7)	162 (11.8)	1.2	1.2	0.9-1.5	0.170
Doctor-diagnosed asthma	165 (12.0)	141 (10.3)	1.2	1.2	0.9-1.5	0.255
Current use of asthma medication	59 (4.3)	44 (3.2)	1.4	1.4	0.9-2.2	0.128
ECRHS definition suggestive of asthma	141 (10.2)	102 (7.5)	1.4	1.4	1.1-1.9	0.021
Air flow limitation						
FEV_1/FVC% <70%	68 (6.4)	93 (8.4)	0.7	0.8	0.5-1.1	0.157
Chronic bronchitis						
Doctor-diagnosed chronic bronchitis	142 (10.3)	116 (8.4)	1.2	1.1	0.9-1.5	0.306
Chronic obstructive bronchitis	11 (1.0)	13 (1.1)	0.9	1.0	0.4-2.3	0.993
Emphysema						
Doctor-diagnosed emphysema	3 (0.2)	2 (0.1)	1.5	n.c.	n.c.	n.c.
Working definition of emphysema	117 (11.1)	121 (11.0)	1.0	1.0	0.8-1.4	0.774

* Odds ratios are adjusted for age, height, smoking pack years (0, <10, 10-20, >20), weight, atopy, rank, service, education and marital status. n.c. = non calculable

12.5.2.1 Atopy

The proportions of Gulf War veterans and comparison group who reacted positively to individual allergens or to any of the allergens were very similar as shown in Table 12.3.

Table 12.3 Prevalence and ORs of atopy

Positive reaction to allergen	GWV n=1347 n (%)	Comp grp n=1353 n (%)	Crude OR	Adj OR	95% CI	P value
Mould mix	48 (3.6)	63 (4.7)	0.8	0.8	0.5-1.1	0.155
House dust mite	569 (43.4)	570 (43.6)	1.0	1.0	0.8-1.1	0.538
Grass mix	400 (30.4)	800 (30.5)	1.0	1.0	0.9-1.2	0.738
Cat dander	177 (13.3)	155 (11.7)	1.2	1.2	0.9-1.5	0.150
Reaction to any of the above	704 (52.3)	712 (52.6)	1.0	1.0	0.8-1.1	0.730

12.5.3 Lung Function Tests (spirometry)

Spirometry was completed by 2682 participants. The complete results of six participants were excluded because their spirograms were technically unacceptable. Blows were excluded from the analysis if they were not meaningful measurements {FEV_1 $\leq$300ml (n=2) or FVC $\leq$200ml (n=2)} and were therefore incompatible with life; or were spuriously elevated {FVC >10,000ml (n=15) or FEV_1 >7,500ml (n=25)}.

The results of the process for evaluating the performance of spirometry according to the ATS criteria are summarised in Table 12.4. In the evaluation of data during this analysis, the ATS criteria were applied sequentially in the order presented in Table 12.4. That is, those who did not meet the criteria for back-extrapolated volume were excluded before the criterion of a minimum of 3 blows was applied. A slightly lower proportion of Gulf War veterans met the ATS criteria overall, and the reproducibility criteria for FVC or FEV_1, than the comparison group.

Table 12.4 Evaluation of spirometry results against ATS criteria

ATS criteria	N=1337 Gulf War veterans n (%)*	N=1339 Comparison group n (%)
Back extrapolated volume (<0.15L or <5% FVC whichever is greater)	1336 (99.9)	1338 (99.9)
Minimum of 3 blows	1279 (95.7)	1301 (97.2)
Reproducibility criteria		
FEV_1 reproducible	1141 (85.3)	1185 (88.5)
FVC reproducible	1096 (82.0)	1143 (85.4)
Both FEV_1 and FVC reproducible	1067 (79.8)	1110 (82.9)

All three ATS criteria were met by 2177/2676 (81.4%) participants. The results of these participants could be used in the analysis of all lung function indices. In total, 2239 (83.7%) subjects met the reproducibility criteria for FVC, and their results were used in the analysis of FVC. Furthermore, 2326 (86.9%) subjects met the reproducibility criteria for FEV_1, and their results were used in the analysis of FEV_1.

Table 12.5 shows the lung function indices compared between study groups. The lung function of Gulf War veterans and the comparison group was very similar. The FEV_1/FVC% ranged from 49% to 99.8% for Gulf War veterans and 51% to 95% for comparison group subjects. The slightly greater FEV_1/FVC%, mean $FEF_{75\%}$ and mean $FEF_{25-75\%}$ measured in Gulf War veterans compared with the comparison group were not considered to be clinically important differences.

There were no differences in the risk of poorer flow indices across subgroups of age, service type, age or rank (data not shown).

Table 12.5 Lung function indices

Parameter	GWV		Comparison group				
	Mean (SD)	**% predicted (SD)**	**Mean (SD)**	**% predicted (SD)**	**Obs diff***	**Adjusted difference between means† (95% CI)**	**P value**
FEV_1, L	4.07 (0.64)	98.0 (13.4)	4.04 (0.64)	97.8 (12.9)	0.03	0.05 (-0.04, 0.05)	0.805
FVC, L	5.13 (0.78)	101.5 (12.6)	5.15 (0.79)	102.8 (12.7)	-0.02	-0.04 (-0.09, 0.01)	0.115
FEV_1/FVC%	79.6 (6.0)	-	78.6 (5.8)	-	1.0	0.7 (0.2, 1.1)	0.008
PEFR, L/min	597.6 (97.8)	105.7 (16.3)	598.2 (93.0)	106.5 (15.5)	-0.6	0.6 (-7.2, 8.4)	0.849
$FEF_{25-75\%}$, L/sec	3.94 (1.12)	90.2 (25.4)	3.79 (1.1)	87.7 (24.3)	0.14	0.06 (-0.03, 0.16)	0.181
$FEF_{75\%}$, L/sec	1.68 (0.61)	78.4 (27.7)	1.57 (0.6)	74.0 (25.9)	0.11	0.05 (0.01, 0.10)	0.024

* Observed differences between means relate to observed lung function values, ie not the predicted values
† Adjusted differences between Gulf War and comparison group means were obtained using robust linear regression, adjusting for age, height, smoking (0, <10, 10-20, >20 pack years), weight, atopy, rank, service, education and marital status.

As shown in Table 12.6, the vast majority of both study groups (approximately 90%) do not have any ventilatory abnormality. Similar proportions of Gulf War veterans and the comparison group have obstructive, restrictive or mixed obstructive and restrictive ventilatory defects.

Table 12.6 Classification of ventilatory abnormalities by spirometry

Ventilatory abnormality	GWV n (%)	Comp grp n (%)	Crude OR	Adj OR	95% CI	P value
None*	968 (90.7)	994 (89.6)	1.0	1.0	-	-
Obstructive ventilatory defect	66 (6.4)	89 (8.2)	0.8	0.8	0.6-1.1	0.186
Restrictive ventilatory defect	31 (3.1)	23 (2.3)	1.4	1.5	0.8-2.6	0.195
Mixed obstructive and restrictive ventilatory defect	2 (0.2)	4 (0.4)	0.5	0.7	0.1-4.2	0.702

* None is the reference category.

12.5.4 Respiratory examination findings

Table 12.7 shows the results of the respiratory physical examination findings for abnormalities that had a prevalence of greater than one percent in the Gulf War veterans. Most individual respiratory examination abnormalities, and a finding of any abnormality, were more common in the Gulf War veterans than the comparison group, and the difference was statistically significant for wheeze.

Table 12.7 Abnormal respiratory examination findings

Respiratory exam finding	GWV N	GWV n	GWV (%)	Comp grp n	Comp grp (%)	Crude OR	Adj OR	95% CI	P value
Pharyngitis	2622	42	(3.1)	35	2.6	1.2	1.2	0.8-1.9	0.429
Tonsils enlarged and/or inflamed*	2609	46	(3.4)	28	2.1	1.7	1.5	0.9-2.5	0.089
Tonsils absent*	2609	256	(18.7)	256	18.9	1.0	1.1	0.9-1.4	0.234
Respiratory rate >20 breaths/min	2634	38	(2.8)	36	2.6	1.1	1.1	0.7-1.7	0.752
Chest shape deformity	2641	21	(1.5)	11	0.8	1.9	1.9	0.9-4.1	0.101
Wheeze	2635	22	(1.6)	8	0.6	2.8	2.6	1.1-5.9	0.029
Other respiratory abnormalities	2618	30	(2.2)	34	2.5	0.9	0.8	1.5-1.4	0.467
Any abnormalities	2618	179	(13.1)	144	10.6	1.3	1.3	1.0-1.6	0.047

* Reference outcome is normal tonsils

12.5.5 Gulf War veteran group subanalysis

The following tables (Table 12.8 to Table 12.13) present the effects of Gulf War service related SMOIL and dust storm exposure, and timing of completion of deployment in relation to the air war, upon selected respiratory conditions and lung function indices. These analyses were confined to Gulf War veterans only.

In addition to the results of sub-analyses presented here, the flow indices of FEV_1/FVC%, PEFR, $FEF_{25-75\%}$ and $FEF_{75\%}$, and the defined outcomes of obstructive and restrictive ventilatory abnormalities were also analysed by these exposure metrics (data not shown). The patterns were similar. The only statistically significant findings relevant to these outcomes related to PEFR and exposure to dust storms, and this is reported below.

Increasing exposure to SMOIL was associated with a decrease in FVC, but was not associated with an increased risk of respiratory conditions, poorer lung function as measured by flow indices, or defined categories of obstructive or restrictive ventilatory defects. 'Any' exposure to SMOIL was associated with a slightly increased risk of emphysema according to the working definition (p=0.015) (Table 12.11) and a small decrease in FVC (p=0.007) (Table 12.13). The statistically significant dose response slope indicates that the adjusted expected decrease in FVC, per categorical increase in SMOIL, was 0.08L (Table 12.13). This difference was small and was not considered to be of clinical significance.

Exposure to dust storms was associated with a slight increase in PEFR (adjusted difference between the means 13.2 L/minute; 95% CI 1.20-25.2, p=0.032). The dose response slope indicated that the adjusted expected increase in PEFR was 13.2 L/minute. This difference was small and was not considered to be of clinical significance. Exposure to dust storms was not associated with increased risk of respiratory conditions, poorer lung function as measured by other flow indices, or defined categories of obstructive or restrictive ventilatory defects.

Gulf War veterans who did not complete their deployment prior to the commencement of the air war were not found to be at increased risk of respiratory conditions, poorer lung function as measured by other flow indices, or defined categories of obstructive or restrictive ventilatory defects, although a slightly increased risk of ECRHS definition suggestive of asthma (Table 12.9) was of borderline statistical significance (p=0.054).

Table 12.8 Subanalysis of Gulf War veterans with doctor-diagnosed asthma by SMOIL and dust storm exposure and completion of deployment prior to the air war

	Gulf War veterans with doctor-diagnosed asthma (N=1359)					
Gulf War exposure	**n**	**%**	**OR**	**Adj OR***	**95% CI**	**P value**
SMOIL						
None	67	11	1.0	1.0	-	
Any	92	13	1.2	1.3	0.9-2.0	
Low	79	13	1.2	1.4	0.9-2.1	
High	13	10	0.9	0.9	0.4-1.8	
Dose response †	-	-	-	1.1	0.8-1.5	0.518
Dust storm						
Absent	80	11	1.0	1.0	-	
Present	84	13	1.2	1.0	0.7-1.5	0.903
Deployment completed before air war						
Yes	32	10	-			
No	133	13	1.3	1.4	0.8-2.2	0.203

* Odds ratios in all the Gulf War sub-analyses are adjusted for service type, rank. age, atopic status, height, weight, education, marital status and smoking (0, <10, 10-20, >20 pack years).
† Dose response is the expected proportionate increase in the odds ratio per category increase in the SMOIL categorisation.

Table 12.9 Sub-analysis of Gulf War veterans with ECRHS definition suggestive of asthma by SMOIL and dust storm exposure and completion of deployment prior to the air war

	Gulf War veterans with ECRHS Asthma (N=1358)					
Gulf War exposure	**n**	**%**	**OR**	**Adj OR**	**95% CI**	**P value**
SMOIL						
None	56	9	1.0	1.0	-	
Any	81	11	1.2	1.2	0.8-1.8	
Low	70	12	1.3	1.3	0.8-1.9	
High	11	9	1.0	0.9	0.4-1.9	
Dose response	-	-	-	1.1	0.8-1.4	0.684
Dust storm						
Absent	63	9	1.0	1.0	-	
Present	77	12	1.4	1.1	0.8-1.7	0.534
Deployment completed before air war						
Yes	22	7	-			
No	119	11	1.7	1.7	1.0-2.9	0.054

Table 12.10 Sub-analysis of Gulf War veterans with doctor-diagnosed bronchitis by SMOIL and dust storm exposure and completion of deployment prior to the air war

	Gulf War veterans with doctor diagnosed bronchitis (N=1358)					
Gulf War exposure	**n**	**%**	**OR**	**Adj OR**	**95% CI**	**P value**
SMOIL						
None	59	10	1.0	1.0	-	
Any	79	11	1.1	1.2	0.8-1.7	
Low	68	11	1.2	1.1	0.7-1.6	
High	11	9	0.9	0.9	0.4-1.9	
Dose response	-	-	-	1.0	0.7-1.4	0.979
Dust storm						
Absent	69	10	1.0	1.0	-	
Present	73	11	1.2	1.1	0.8-1.7	0.501
Deployment completed before air war						
Yes	31	10	-			
No	111	11	1.1	1.1	0.7-1.7	0.690

Table 12.11 Sub-analysis of Gulf War veterans with working definition of emphysema by SMOIL and dust storm exposure and completion of deployment prior to the air war

	Gulf War veterans with working definition of emphysema (N=1043)					
Gulf War exposure	**n**	**%**	**OR**	**Adj OR**	**95% CI**	**P value**
SMOIL						
None	42	9	1.0	1.0	-	
Any	72	13	1.6	1.7	1.1-2.6	
Low	63	14	1.7	1.9	1.2-3.0	
High	9	10	1.2	1.1	0.5-2.8	
Dose response	-	-	-	1.4	1.0-1.9	0.071
Dust storm						
Absent	59	11	1.0	1.0	-	
Present	57	11	1.1	0.9	0.6-1.4	0.758
Deployment completed before air war						
Yes	22	9	-			
No	95	12	1.4	1.4	0.8-2.4	0.180

Table 12.12 Sub-analysis of mean FEV_1 of Gulf War veterans by SMOIL and dust storm exposure and completion of deployment prior to the air war

	FEV_1 (N=1127)					
Gulf War exposure	**Mean**	**(SD)**	**Diff**	**Adj Diff**	**95% CI**	**P value**
SMOIL						
None	4.09	0.64	0.0	0.0	-	
Any	4.05	0.64	-0.04	-0.05	-0.11, 0.01	
Low	4.06	0.66	-0.03	-0.05	-0.11, 0.02	
High	4.04	0.60	-0.05	-0.03	-0.15, 0.08	
Dose response	-	-	-	-0.03	-0.08, 0.02	0.252
Dust storm						
Absent	4.08	0.60	0.0	0.0		
Present	4.06	0.65	-0.03	-0.03	-0.09, 0.03	0.369
Deployment completed before air war						
Yes	4.08	0.67	0.0			
No	4.07	0.63	-0.01	-0.06	-0.13, 0.01	0.102

Table 12.13 Sub-analysis of mean FVC of Gulf War veterans by SMOIL and dust storm exposure and completion of deployment prior to the air war

	FVC (N=1083)					
Gulf War exposure	**Mean**	**(SD)**	**Diff**	**Adj Diff**	**95% CI**	**P value**
SMOIL						
None	5.17	0.77	0.0	0.0	-	
Any	5.10	0.79	-0.07	-0.10	-0.18, -0.03	
Low	5.11	0.81	-0.06	-0.08	-0.16, 0.004	
High	5.03	0.66	-0.14	-0.14	-0.28, 0.003	
Dose response	-	-	-	-0.08	-0.14, 0.02	0.014
Dust storm						
Absent	5.16	0.77	0.0	0.0	-	
Present	5.10	0.80	-0.05	-0.05	-0.12, 0.02	0.188
Deployment completed before air war						
Yes	5.11	(0.80)	0.0	0.0		
No	5.14	(0.78)	0.03	-0.05	-0.14, 0.04	0.261

12.6 Discussion

In this chapter, we compared respiratory health outcomes in Gulf War veterans and the comparison group according to respiratory symptoms, definitions of respiratory conditions

that utilised combinations of respiratory symptoms and indices of lung function or use of asthma medication, spirometry results and recognised categories of ventilatory abnormalities.

The main findings are that Gulf War veterans report more respiratory symptoms than the comparison group, and more asthma according to the European Community Respiratory Health Survey but not other definitions. Gulf War veterans were found to have more abnormalities on respiratory examination, notably wheeze. Gulf War veterans and the comparison group have very similar lung function when several different parameters, based on spirometry, were considered.

A variety of approaches have been used to define asthma in epidemiological studies including self-reported symptoms or a combination of symptoms, doctor diagnosis of asthma, current use of medication for asthma and spirometry. It has been recognised that a single definition of asthma is not applicable to all studies, and that the focus of epidemiological research should be on comparing the prevalence of asthma between populations using standardised methods than on trying to estimate the "actual prevalence of asthma" in a population.[378]

The analyses of respiratory health outcomes in our study have utilised this approach of comparing groups using various definitions. However, there are limitations to the comparisons that can be made across the various definitions used. One problem is the differing time periods to which the definitions relate. For example, doctor-diagnosed chronic bronchitis related to “ever” having chronic bronchitis that was confirmed by a doctor. The proportions of the study groups reporting this condition are 8-10 times higher than those defined as having chronic obstructive bronchitis that was defined by persistent cough over that last 2 years and current physiological evidence of airflow limitation. Conversely, emphysema is often underdiagnosed in clinical practice, and very few study participants reported doctor-diagnosed emphysema “ever”. Eleven times as many participants in each study group were defined as having emphysema according to a working definition that included current symptoms of shortness of breath and physiological evidence of airflow limitation. However this definition includes some individuals who lack physical fitness and others with unrecognised cardiac disease.

Furthermore, the definitions based on “ever”, such as doctor-diagnosed asthma, doctor-diagnosed chronic bronchitis and doctor-diagnosed emphysema, do not just relate to the post Gulf War period. As presented in the General Health chapter of this report, self-reported asthma that had its onset in 1991 or later and was considered by a HSA doctor to be a possible or probable diagnosis was reported in a similar proportion of Gulf War veterans and comparison group subjects. In addition, current use of asthma medication suggests that asthma is a current condition in a similar proportion of the study groups.

The findings with respect to particular respiratory conditions were not consistent. The ECRHS definition suggestive of asthma incorporates symptoms of asthma over the last 12 months and current use of asthma medication. More Gulf War veterans reported a condition suggestive of asthma according to this standardised definition than the comparison group. However, when spirometry results formed the basis of comparison between study groups, the proportions who demonstrated airflow limitation (as defined by FEV_1 <70%) or an obstructive ventilatory abnormality decreased, and did not differ between the study groups. Asthma is a respiratory condition characterised by variable airflow obstruction, and the proportions based on FEV_1 <70% relate to their respiratory function at the time of the actual HSA medical assessment. Thus, although the absolute proportions that were defined as having asthma differed according to the definitions used, the relative proportion of the two study groups who have asthma based on most of these definitions was similar.

Respiratory examination abnormalities were more common in the Gulf War veteran group, notably wheeze. This finding of increased wheeze in the Gulf War veteran group is consistent with the greater current use of asthma medications by the Gulf War veterans, but not with the better small airways function.

Lung function was similar between groups. Gulf War veterans had a slightly higher late-flow ($FEF_{75\%}$) indicating better small airways lung function. Even though this difference between the groups for $FEF_{75\%}$ was statistically significant, in clinical terms the difference was small and probably unimportant. Any effects of exposures such as SMOIL were not reflected in reductions to $FEF_{25-75\%}$, $FEF_{75\%}$ or FEV_1 that would be consistent with a picture of greater airflow limitation in Gulf War veterans.

There were no apparent differences in the risk of respiratory conditions, poorer flow indices or most respiratory symptoms across subgroups of age, service type or rank. Although the Army subgroup was at higher risk of wheeze and officers were at lower risk of morning sputum, there was no obvious explanation for this and they may have been chance or isolated findings, especially as this analysis involved multiple comparisons.

In overseas cross-sectional studies since the Gulf War, Gulf War veterans have also been found to report respiratory symptoms more commonly than non-Gulf comparison groups.[20, 22, 157] Iowa Gulf War veterans have reported significantly more respiratory conditions according to definitions based on combinations of self-reported symptoms of asthma (7.2% vs 4.1%) and bronchitis (3.7% vs 2.7%) than the comparison group.[16] British Gulf War veterans were also more likely to report medical conditions such as asthma (6.5% vs 3.7%) and bronchitis (4.4% vs 2.2%) over the last 12 months compared with the non-Gulf comparison groups.[21] US Gulf War veterans, in another study, reported more sinusitis, bronchitis and other lung conditions, but similar rates of asthma in the last 12 months.[20]

Many of the conclusions of other epidemiological studies of Gulf War veterans' respiratory health have been based solely on self-reported findings of postal or telephone questionnaire surveys. The use of spirometry in our study has increased the objectivity of measurement, but there are limited respiratory health data from other cross-sectional studies of Gulf War veterans with which to compare our results. The only previous cross-sectional study to undertake lung function testing was the Danish Gulf War veterans' study.[162] They found no significant differences in lung function related to expected values between the Gulf War veterans and non-Gulf comparison group for FVC, FEV_1 or Peak Flow.

One of the strengths of our study was to collect data on exposure to SMOIL and dust storms during the Gulf War service and explore the relationship between these exposures and respiratory health outcomes.

Gulf War veterans who were exposed to 'any' SMOIL have an increased risk of emphysema according to the working definition used in the study. Gulf War veterans who were exposed to 'any' SMOIL also had a slightly worse FVC, but the differences were small. A dose response relationship was evident for exposure to SMOIL, but the small differences found were not considered to be clinically important at this stage. Typically, emphysema affects FEV_1 more than FVC, so these findings are inconsistent. Gulf War veterans who were exposed to dust storms, have a slightly better PEFR, but the difference was also small and not considered to be clinically important. Gulf War veterans who were exposed to dust storms do not have more respiratory conditions, poorer lung function or ventilatory abnormalities as defined in our study than the Gulf War veterans who were not exposed to dust storms. There was no significant increase in risk of respiratory conditions, poorer lung function as measured

by other flow indices, or defined categories of obstructive or restrictive ventilatory defects in Gulf War veterans who did not complete their deployment prior to the commencement of the air war, and thus had the potential to be exposed to SMOIL. When we analysed on the basis of the more objective measure of SMOIL exposure, ie deployed during or after the air war started, the only association was with ECRHS asthma, and this was of borderline significance.

We used ATS criteria for the standardisation of the performance and evaluation of spirometry.[298] The ATS criteria were primarily developed for clinical settings, but their application has been extended to epidemiological studies. A clinical setting or single lung function laboratory provides quite a different setting for the performance of spirometry in comparison to a large multicentre study, such as ours, with different data collectors at nine different HSA offices. Measures to standardise the performance of spirometry included the use of standardised equipment (the SpiroCard spirometer) and daily calibration, training for HSA nurses prior to their commencement as data collectors for the study, ongoing monitoring of the performance of spirometry, and additional spirometry training during the study to address issues that were detected as part of our ongoing evaluation of the study's progress. In our study, 13.1% of subjects who undertook spirometry did not meet the ATS criteria for FEV_1, 16.3% did not meet the ATS criteria for FVC, and 18.6% did not meet the full ATS criteria. The proportions of the study groups who fulfilled the ATS criteria were slightly lower in the Gulf War veteran group.

The proportion of subjects who are unable to perform acceptable spirometry varies considerably across studies.[379-383] The proportions in our study are a little higher than those found in other multicentre respiratory studies, in which test-failure (as measured by criteria that varied but included a measure of FEV_1 reproducibility) of between 8-11%[380, 381, 383] has been reported. A multicentre study of 8,522 white adults in 6 US cities[379] found that of the 8,364 who performed spirometry in the study, 747 (8.9%) had an unacceptable FEV_1, 534 (6.4%) had an unacceptable FVC, and 235 (2.8%) had both FEV_1 and FVC unacceptable according to ATS reproducibility criteria of blows within 100ml or 5% of each other whichever was greater. When an alternative less restrictive definition was used for reproducibility of FEV_1 and FVC, fewer results were considered non-reproducible (2.6% were unacceptable on FEV_1 and 1.4% were unacceptable on FVC). The criteria for our study included criteria of a back-extrapolated volume <0.15 L and minimum of 3 blows in addition to reproducibility criteria for FEV_1 and FVC. In the circumstances of our study, we have taken a conservative approach, similar to that taken in other studies, to the application of ATS criteria in excluding spirometry tests. The non-reproducibility was slightly greater in the Gulf War veteran group. This is of some concern because it could reflect a higher prevalence of respiratory disease in Gulf War veterans.

Lung function test failure, as evidence by non-reproducibility of blows and failure to meet the ATS criteria, may be a marker of respiratory impairment. Eisen *et al*[379] investigated the relationship between six chronic respiratory symptoms and the performance of a non-reproducible FEV_1. Breathlessness and asthma were associated with FEV_1 non-reproducibility in men and women, and non-reproducibility of FEV_1 was almost as strong a predictor of mortality as poor FEV_1.

Part of the problem may have been that the participants in our study who had most difficulty with the performance of spirometry had worse lung function or other medical or psychological conditions that affected their ability to perform spirometry. We would like to undertake further evaluation to assess the profile of those who were unable to perform

spirometry according to the ATS criteria, and consider ways to enhance performance of spirometry in future multicentre national epidemiological studies of veterans.

Further investigation and confirmation of respiratory conditions defined in this study would involve assessment of the reversibility of airflow obstruction. This could be assessed by performing spirometry before and after administration of a bronchodilator, such as salbutamol, by metered dose inhaler or nebuliser. Alternatively bronchial hyperreactivity could be measured by methacholine or histamine challenge testing. The clinical diagnosis of emphysema is not physiological or symptom based and requires an assessment of gas transfer factor or an imaging modality such as chest CT scan. More detailed assessments of lung structure and function, such as these, were beyond the scope of this cross-sectional study.

The general evaluation of participation bias in our study (see Recruitment chapter) has shown that effects on odds ratios for binary health outcomes are likely to be small and therefore participation bias is unlikely to explain the differences (or lack thereof) that we found in respiratory health status between the Gulf War veterans and the comparison group. More directly, application of the non-participation imputation procedure detailed in the Recruitment chapter to the examination of differences in prevalence of doctor diagnosed asthma between Gulf War veterans and comparison group subjects revealed only minimal effects of non-participation. The mean of the age, rank and service-adjusted odds ratios from the imputation procedure correcting for non-participation was 1.14, which is only marginally lower than the corresponding odds ratio of 1.15 among participants. The findings for other respiratory outcomes would likely be similar in effect. However, some caution should be applied to the interpretation of these analyses as they are based on statistical models with underlying assumptions and the representativeness of the SF-12 data from the telephone-questionnaire participants (see Recruitment chapter for more detail).

Information bias is another form of bias that may have affected the results of these analyses, as Gulf War veterans may be more susceptible to influences from the media on self-reporting of respiratory symptoms or conditions. This source of bias would not have affected the results of objective measures of physical health used to assess the respiratory health status of both groups such as the spirometry or definitions of ventilatory abnormalities.

Confounding may also have influenced the results. We controlled for age, rank, service type, education and marital status as a core set of confounders as well as other factors such as smoking in pack years, atopy, height and weight that are known to increase the risk of respiratory disease or affect lung function. It is possible that other unidentified confounders, such as work exposures, may have impacted on the results.

Although there are some limitations to the approach used in these analyses, a strength of these analyses is the use of a comparison group to whom the same definitions were applied.

12.6.1 Summary of findings

In summary, and in answer to the research questions of the study, Gulf War veterans report more respiratory symptoms than the comparison group. Gulf War veterans report more respiratory conditions according to the ECRHS definition suggestive of asthma, but do not report other respiratory conditions more commonly according to the definitions used in our study. A greater proportion of Gulf War veterans had chest wheeze detected on physical examination.

Gulf War veterans do not have poorer lung function than the comparison group based on the spirometry measures used in our study. A slightly lower proportion of Gulf War veterans

were able to perform acceptable spirometry according to the American Thoracic Society criteria used in this study, and this could reflect a higher prevalence of respiratory disease in Gulf War veterans and may predict more respiratory disease in the future.

Gulf War veterans who were exposed to SMOIL have a slightly worse FVC than the comparison group, but this difference is not considered to be clinically significant. Gulf War veterans who were exposed to dust storms have slightly better PEFR than the comparison group, but this difference is also not considered to be clinically significant. Gulf War veterans who were in the Gulf at or after the start of the burning oil wells had a small increase in ECRHS asthma, but were not at significantly increased risk of other respiratory conditions, poorer lung function or ventilatory abnormalities than Gulf War veterans who did complete their deployment prior to this time.

13. Neurological health

13.1 Aim

The aim of these analyses is to investigate whether male Australian Defence Force personnel who served in the Gulf War have a higher rate of adverse neurological health outcomes than the comparison group; and, if so, are these associated with exposures and experiences that occurred in the Gulf War?

13.2 Research questions

1. Do Australian Gulf War veterans have more neuropathic symptoms than the comparison group?
2. Do Australian Gulf War veterans have more symptoms or physical signs that are indicative of a neuropathic disorder than the comparison group?
3. Do Australian Gulf War veterans have more symptoms or physical signs that are indicative of adverse neurological health outcomes such as myopathy, disorders of peripheral motor neurones or their axons, or a central nervous system disorder, including epilepsy, than the comparison group?
4. Where differences in risk of adverse neurological health outcomes occur between Gulf War veterans and the comparison group, are these associated with exposures and experiences that occurred in the Gulf War?

13.3 Definition of neurological health outcomes

The definitions of neurological health outcomes used to compare the Gulf War veterans and comparison group in these analyses used combinations of neurological symptoms and/or signs that may suggest that a particular sort of neurological disorder was present. The definitions for these neurological health outcomes were based on neuropathic symptoms that were self-reported in the postal questionnaire and neurological signs that were assessed by HSA doctors during the physical examination. The definitions for this study were developed in consultation with a neurologist, and, where possible, were based on instruments used in other studies. The neurological health outcomes defined were:

- Neuropathic symptoms
- Neuropathic disorder
- Myopathy
- Disorders of peripheral motor neurones or their axons
- Central nervous system disorder
- Epilepsy

13.3.1 Neuropathic symptoms definition

Neuropathic symptoms that had occurred in the past month were self-reported in the postal questionnaire (Recent health symptoms. G20, q64-80).

13.3.2 Neuropathic disorder definition

Two approaches were used to define neuropathic disorders. The first approach defined neuropathic disorders according to self-reported neuropathic symptoms that had occurred in the past month, and according to combinations of self-reported neuropathic symptoms that

had occurred in the past month and neurological signs. The second approach, the neuropathy impairment score, utilised a composite score that was based on aspects of the neurological examination, and did not include neuropathic symptoms.

13.3.2.1 A neuropathic disorder defined by neuropathic symptoms and neurological signs

Neuropathic disorders tend to affect the lower limbs before the upper limbs, and people often report symptoms before signs are detectable on physical examination. Therefore, four operational definitions of increasing specificity were used to report the prevalence of a neuropathic disorder:

1. **lower limb neuropathic symptoms** = numbness, "asleep feeling" or prickling sensation in your feet or legs,
2. **lower and upper limb neuropathic symptoms** = numbness, "asleep feeling" or prickling sensation in your feet or legs and numbness, "asleep feeling" or prickling sensation in your hands or arms
3. **lower limb neuropathic symptoms and signs** = numbness, "asleep feeling" or prickling sensation in your feet or legs, and
   - one or more symptoms of gait unsteadiness, and
   - one or more signs of abnormal sensation in the big or little toe on either foot or one or more signs of reduced or absent ankle reflexes on either foot.
4. **more severe lower limb neuropathic symptoms and signs** = numbness, "asleep feeling" or prickling sensation in your feet or legs and
   - two or more symptoms of gait unsteadiness, and
   - either two or more signs of abnormal sensation in the big or little toe on either foot, or one or more signs of abnormal sensation in the big or little toe on either foot and one or more signs of reduced or absent ankle reflexes on either foot.

13.3.2.2 A neuropathic disorder defined by a neuropathy impairment score

The neuropathy impairment score was based on scoring specific components of the neurological examination that was done by HSA doctors. This definition of neuropathic deficits through a neuropathy impairment score was based on the Mayo Clinic method of the Neuropathy Impairment Score that was developed and modified by Dyck *et al*[384, 385] from the Neurologic Disability Score.[273, 384-387] It is a global score of muscle weakness and reflex and sensory abnormalities indicative of neuropathy based on a neurological examination. This approach of generating a summary score has been used in several studies for comparing study groups.[384, 386-390]

The scoring system of the Neuropathy Impairment Score was adapted and applied *post hoc* to the relevant components of the neurological examination performed by HSA doctors according to a standardised procedure. The components were scored in the following manner for the right and left sides of the body, and combined into a score for each person. The mean scores for Gulf War veterans and the comparison group were then compared.

For calculating the neuropathy impairment score:

- Cranial nerves were scored as:
  - 3rd cranial nerve, 0 = normal or 2 = abnormal
  - 6th cranial nerve, 0 = normal or 2 = abnormal
  - facial weakness, 0 = normal, 2 = weak or 4 = absent facial movements

– tongue weakness, 0 = normal or 2 = weak tongue movements.

- Muscle weakness was scored as:

  – 0 = normal power, 1 = active movement against gravity and resistance, 2 = active movement against gravity, 3 = active movement, with gravity eliminated, and 4 = flicker of trace of contraction or no contraction for each of 17 upper and lower limb muscle groups.

- Reflexes were scored as:

  – 0 = normal, 1 = reduced and 2 = absent for each of the biceps, triceps, brachioradialis, quadriceps and ankle reflexes.

- Sensation was scored as:

  – 0 = normal, 1 = decreased and 2 = absent for pinprick sensation of each of the thumb and big toe.

  – 0 = normal and 1 = decreased for vibratory and joint position sensation of each of the index finger and big toe.

13.3.3 Myopathy definition

Myopathy was defined as:

- difficulty lifting objects above your head, or from a high shelf and weakness of shoulder abduction or elbow flexion on either side or
- difficulty getting up from sitting in a chair or couch without the use of your arms and weakness of hip flexion or knee flexion on either side,

  and
- absence of tremor, normal reflexes, down going or equivocal plantar reflexes, normal upper or lower limb muscle tone, and normal sensation.

13.3.4 Disorders of peripheral motor neurones or their axons definition

Symptoms and signs indicative of disorders of peripheral motor neurones or their axons were defined as:

- one or more symptoms of muscle weakness of difficulty lifting objects above your head or from a high shelf, difficulty undoing buttons, difficulty turning doorknobs or unscrewing jars, difficulty getting up from sitting in a chair or couch without the use of your arms, problems with tripping or your feet slapping, while walking, or difficulty swallowing food (more than occasionally), and
- one or more signs of muscle fasciculations or muscle wasting or muscle weakness in any muscle group, and
- no symptoms of sensory disturbance or difficulty recognising hot from cold water; difficulty feeling pain, cuts or injuries; numbness, “asleep feeling” or prickling sensation in your hands or arms; numbness, “asleep feeling” or prickling sensation in your feet or legs; burning, deep aching pain or tenderness in your hands or arms; burning, deep aching pain or tenderness in your feet or legs; unusual sensitivity or tenderness of your skin when clothes or bedclothes rub against you, and
- normal sensation.

13.3.5 Central nervous system disorder definition

Symptoms and signs indicative of a central nervous system disorder were defined as:

- one or more symptoms of fatigue, loss of concentration, tingling or burning sensation in hands or feet, loss of sensation in hands or feet, problems with sexual functioning, loss of balance or coordination, loss of control over bladder or bowels, double vision or passing urine more often or one or more symptoms of muscles weakness and
- one or more signs of:
  - increased tone in the upper or lower limb and increased reflexes in the upper or lower limb or upgoing plantar reflex and decreased power in any muscle group on the same side of the body, or
  - sensory abnormality in the upper and lower limbs or nipple or umbilicus level and decreased or absent sensation in the big or little toe on the same side of the body and normal or increased reflexes on the same side, or
  - coordination abnormality of the finger nose or heel-shin test.

13.3.6 Epilepsy definition

Epilepsy was defined as:
- a response indicating that seizures or convulsions were experienced in the past month or
- self-reported epilepsy that had been diagnosed in 1991 or since and was rated as a possible or probable diagnosis by a HSA doctor.

13.4 Results

13.4.1 Neuropathic symptoms and disorders

13.4.1.1 Neuropathic symptoms

Figure 13.1 shows that Gulf War veterans reported more neuropathic symptoms than the comparison group consistently, whatever the number of neuropathic symptoms. Both study groups had a small proportion of subjects who reported a large number of symptoms.

Figure 13.1 Total number of neuropathic symptoms reported

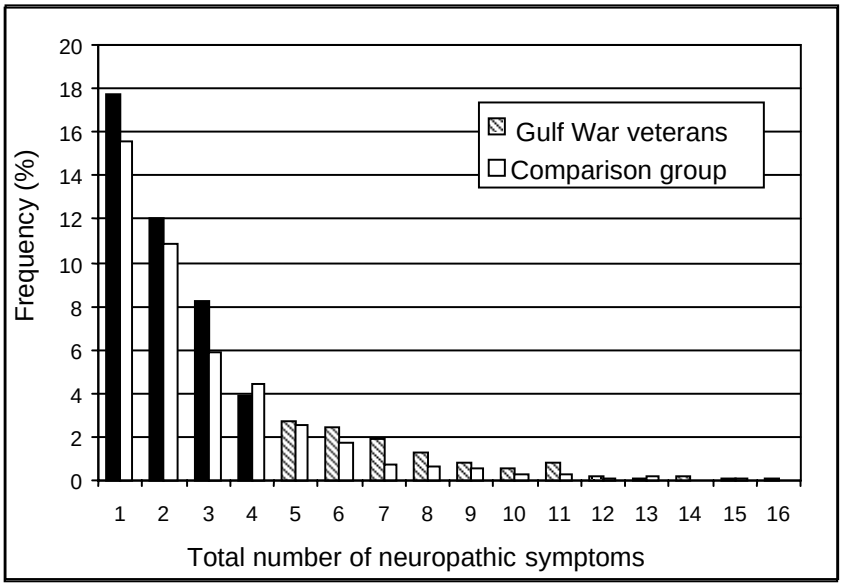


Table 13.1 presents the proportion of Gulf War veterans who self-reported neuropathic symptoms in the past month, which are subgrouped according to whether they are predominantly symptoms of muscle weakness, sensory disturbance or autonomic dysfunction. Although some symptoms such as difficulty undoing buttons, difficulty turning doorknobs/unscrewing jars and problems with tripping, or feet slapping, while walking can be symptoms of either a sensory disturbance or muscle weakness, they have been categorised according to the deficit of which they are most characteristic.

Fewer Gulf War veterans reported no neuropathic symptoms (47.0 vs 56.3%) (Table 13.1). Gulf War veterans reported all individual neuropathic symptoms more commonly, and more neuropathic symptoms overall, than the comparison group. Furthermore, Gulf War veterans reported more total symptoms of muscle weakness, sensory disturbance, and autonomic dysfunction than the comparison group. Adjustment for potential confounders made little difference to the odds ratios.

Table 13.1 Prevalence and odds ratios (ORs) of neuropathic symptoms in the past month

	GWV n (%)	Comp grp n (%)	Crude OR	Adj OR*	95% CI	P value
Neuropathic symptoms						
≥1 neuropathic symptom	753 (53.0)	676 (43.7)	1.5	1.4	1.2-1.7	<0.001
0 neuropathic symptoms	669 (47.0)	871 (56.3)				
1 neuropathic symptom	252 (17.7)	241 (15.6)				
2 neuropathic symptoms	171 (12.0)	168 (10.9)				
3 neuropathic symptoms	116 (8.2)	91 (5.9)				
≥4 neuropathic symptoms	214 (15.0)	176 (11.4)				
Symptoms of muscle weakness						
≥1 symptom of muscle weakness	417 (29.3)	395 (25.5)	1.2	1.2	1.0-1.4	0.013
Difficulty lifting objects above head	193 (13.6)	179 (11.6)	1.2	1.3	1.0-1.6	0.048
Difficulty undoing buttons	45 (3.2)	31 (2.0)	1.6	1.7	1.1-2.8	0.027
Difficulty turning doorknobs/unscrewing jars	72 (5.1)	58 (3.8)	1.5	1.5	1.1-2.2	0.026
Difficulty getting up from sitting in a chair	293 (20.6)	276 (17.9)	1.3	1.6	1.1-2.4	0.014
Problems with tripping, or feet slapping, while walking	94 (6.6)	74 (4.8)	1.4	1.4	1.0-2.0	0.035
Difficulty swallowing food (more than occasionally)	35 (2.5)	26 (1.7)	1.5	1.4	0.8-2.4	0.179
Symptoms of sensory disturbance						
≥1 symptom of sensory disturbance	654 (46.0)	558 (36.1)	1.5	1.5	1.3-1.7	<0.001
Difficulty recognising hot from cold water	12 (0.8)	11 (0.7)	1.2	1.4	0.6-3.2	0.484
Difficulty feeling pain, cuts or injuries	45 (3.2)	20 (1.3)	2.5	2.7	1.5-4.6	0.001
Numbness, “asleep feeling” or prickling sensation in hands or arms	367 (25.9)	278 (18.0)	1.6	1.6	1.3-1.9	<0.001
Numbness, “asleep feeling” or prickling sensation in feet or legs	306 (21.6)	248 (16.1)	1.4	1.4	1.2-1.7	<0.001
Burning, deep aching pain or tenderness in hands or arms	108 (7.6)	84 (5.4)	1.4	1.5	1.1-2.0	0.016
Burning, deep aching pain or tenderness in feet or legs	164 (11.5)	141 (9.1)	1.3	1.3	1.1-1.7	0.019
Unusual sensitivity or tenderness of your skin when clothes or bedclothes rub against you	100 (7.0)	58 (3.8)	1.9	2.0	1.4-2.8	<0.001
Feeling unsteady walking on uneven ground	103 (7.2)	87 (5.6)	1.3	1.4	1.0-1.4	0.047
Feeling unsteady walking in the dark	142 (10.0)	96 (6.2)	1.7	1.7	1.3-2.2	<0.001
Feeling like you may fall over because of unsteadiness	81 (5.7)	60 (3.9)	1.5	1.5	1.1-2.2	0.019
Symptom of autonomic dysfunction						
Feeling faint when standing up from lying or sitting	187 (13.2)	144 (9.3)	1.5	1.4	1.1-1.7	0.011

* Odds ratios (OR) are adjusted for age, rank and service type at deployment, current marital status, highest level of education, alcohol (AUDIT score >8) and a history of diabetes.

The mean total number of self-reported neuropathic symptoms was used as a summary measure of neuropathic symptoms that were self-reported by the study groups, in a manner similar to that used for general health symptoms in the General Health chapter. Table 13.2 shows that the mean total number of symptoms reported by Gulf War veterans was 40 per cent higher than that of the comparison group. The mean total number of self-reported neuropathic symptoms was also greater for Gulf War veterans when the study groups were broken into subgroups of service type, rank and age. The mean total number of neuropathic symptoms was similar across the age subgroups for Gulf War veterans. There was no increase in risk of neuropathic symptoms across subgroups of age, rank or service type.

Table 13.2 Total number of neuropathic symptoms

	Total number of neuropathic symptoms				
	GWV	**Comp grp**	**Crude ratio of means**	**Adjusted ratio of means (CI)**	**P value**
	Mean (SD)	**Mean (SD)**			
Total study population	1.7 (2.5)	1.2 (2.0)	1.4	1.4 (1.2-1.5)	<0.001
					P value for interaction
Service type					
Navy	1.7 (2.5)	1.2 (1.9)	1.4	1.4 (1.2-1.6)	P=0.241
Army	2.1 (2.5)	1.9 (2.7)	1.1	1.1 (0.8-1.4)	
Air Force	1.1 (2.4)	0.8 (1.7)	1.5	1.5 (0.9-2.4)	
Rank					
Officer	1.0 (1.6)	0.8 (1.6)	1.4	1.4 (1.0-1.8)	P=0.582
Other ranks - supervisory	1.8 (2.6)	1.5 (2.2)	1.3	1.3 (1.1-1.5)	
Other ranks – non supervisory	1.8 (2.7)	1.2 (2.0)	1.5	1.5 (1.2-1.9)	
Age					
<20 years	1.7 (2.5)	0.8 (1.5)	1.9	1.9 (1.3-2.8)	P=0.449
20 - <25 years	1.5 (2.3)	1.1 (1.9)	1.3	1.3 (1.1-1.7)	
25 - <35 years	1.6 (2.5)	1.2 (2.0)	1.3	1.3 (1.1-1.6)	
≥ 35 years	1.9 (2.8)	1.6 (2.6)	1.3	1.3 (1.0-1.8)	

13.4.1.2 Neuropathic disorders

Gulf War veterans generally reported more neuropathic disorders according to the operational definitions. The exception to this was 'more severe lower limb signs and symptoms' where the numbers were small (Table 13.3).

Table 13.3 Prevalence and ORs of increasingly specific definitions of a neuropathic disorder

Case definition	GWV n (%)	Comp grp n (%)	Crude OR	Adj OR	95% CI	P value
Lower limb neuropathic symptoms	306 (21.6)	248 (16.1)	1.4	1.4	1.2-1.7	0.001
Lower and upper limb neuropathic symptoms	212 (15.0)	145 (9.4)	1.7	1.7	1.3-2.1	<0.001
Lower limb neuropathic symptoms and signs	42 (3.0)	30 (2.2)	1.4	1.6	1.0-2.7	0.054
More severe lower limb neuropathic symptoms and signs	11 (0.8)	11 (0.8)	1.00	1.4	0.6-3.3	0.481

The mean neuropathy impairment score was similar in the study groups (Table 13.4). Similar proportions of Gulf War veterans (65.2%) and comparison group subjects (66.4%) had a neuropathy impairment score of zero. The mean neuropathy impairment score (SD) was similar on both the right and left sides of the body, with a left side neuropathy impairment score of 1.04 (2.3) vs 1.00 (2.5) and a right side neuropathy impairment score of 0.99 (2.3) vs 1.04 (2.6) for the Gulf War veteran and comparison groups respectively. The mean neuropathy impairment score increased with age in both study groups. There was no difference in risk of a higher score across subgroups of service type, rank or age.

Table 13.4 Mean neuropathy impairment score

	Mean total neuropathy impairment score				
	GWV	Comp grp	Crude ratio of means	Adjusted ratio of means (CI)	P value
	Mean (SD)	Mean (SD)			
Total study population	2.0 (4.3)	2.0 (4.7)	1.0	1.1 (0.9-1.3)	P=0.510
					P value for interaction
Service type					
Navy	2.0 (4.1)	2.0 (4.7)	1.0	1.1 (0.9-1.3)	}p=0.287
Army	2.5 (6.8)	3.1 (5.5)	0.8	0.7 (0.4-1.2)	
Air Force	2.0 (4.2)	1.4 (3.9)	1.4	1.2 (0.7-2.3)	
Rank					
Officer	1.3 (3.1)	1.3 (3.3)	1.0	1.1 (0.7-1.6)	}p=0.757
Other ranks - supervisory	2.4 (4.9)	2.5 (5.5)	1.0	1.0 (0.8-1.3)	
Other ranks – non-supervisory	1.8 (3.9)	1.6 (4.1)	1.1	1.2 (0.8-1.6)	
Age					
<20 years	1.4 (3.4)	1.5 (3.5)	0.9	0.9 (0.5-1.6)	}p=0.903
20 - 24 years	1.7 (3.6)	1.7 (4.3)	1.0	1.0 (0.7-1.5)	
25 - <35 years	2.3 (4.5)	2.1 (4.9)	1.1	1.1 (0.9-1.4)	
≥ 35 years	2.4 (5.6)	2.4 (4.9)	1.0	1.1 (0.7-1.8)	

13.4.2 Symptoms or signs indicative of myopathy, disorders of peripheral motor neurones or their axons, central nervous system disorder and epilepsy

While Gulf War veterans had slightly more neurological symptoms and signs that are indicative of myopathy, a central nervous system disorder and epilepsy than the comparison group, these differences were statistically significant for central nervous system disorder only (Table 13.5). A slightly lower proportion of Gulf War veterans had neurological symptoms and signs that were indicative of disorders of peripheral motor neurones or their axons compared with the comparison group, but the difference was not statistically significant. The number of defined cases in each study group was small, and this limited the power of the study to make further comparisons (Table 13.5).

Table 13.5 Prevalence and ORs of operational definitions of symptoms and signs indicative of myopathy, disorders of peripheral motor neurones or their axons, a central nervous system disorder and epilepsy

Case definition of neurological condition	GWV n (%)	Comp grp n (%)	Crude OR	Adj OR	95% CI	P value
Myopathy	18 (1.3)	13 (1.0)	1.4	1.4	0.7-3.0	0.375
Disorders of peripheral motor neurones or their axons	20 (1.5)	27 (2.0)	0.7	0.9	0.5-1.6	0.622
Central nervous system disorder	35 (2.5)	21 (1.5)	1.7	1.8	1.0-3.1	0.045
Epilepsy	8 (0.6)	5 (0.3)	1.7	1.8	0.6-5.9	0.331

Other neurological examination signs not included in these above definitions included tremor and gait problems. These were found in similar proportions in the study groups. Tremor is found in central nervous system disorders, but can also have a number of other causes. Tremor was found in 2.4% of Gulf War veterans and 2.2% of comparison group subjects. Gait problems can occur in both central nervous system and peripheral neurological disorders, and thus do not differentiate well between these types of disorders. Gait problems were found in 2.1% of Gulf War veterans and 2.2% of comparison group subjects.

13.4.3 Gulf War veteran group subanalysis

The following tables (Table 13.6, Table 13.7, Table 13.8) present the effects of Gulf War service related exposures upon selected neurological health outcomes. These analyses were confined to Gulf War veterans only.

Reporting of ‘any’ neuropathic symptoms was associated with several exposures examined in these subanalysis including antimalarials, anti-biological warfare tablets, solvents, pesticides/insecticides and repellents, but not with some other exposures such as having taken ‘any’ pyridostigmine tablets or clustering of immunisations (Table 13.6). Reporting of ‘any’ neuropathic symptoms was also associated with immunisations, pyridostigmine bromide, antimalarials, and anti-biological warfare tablets in those subjects who reported that they did not know the number of immunisations received, or whether they had taken pyridostigmine

bromide, antimalarials or anti-biological warfare tablets. Increasing number of immunisations received and increasing number of pyridostigmine bromide tablets were weakly associated with 'any' neuropathic symptoms in a dose response relationship. For example, the dose response slope for immunisations indicates that the adjusted expected increase in 'any neuropathic symptoms' per unit increase in the number of immunisations was 5%. The dose response slope for pyridostigmine bromide indicates that the adjusted expected increase in 'any neuropathic symptoms' per categorical increase in the number of pyridostigmine bromide tablets taken was 10%.

Table 13.6 Subanalysis of Gulf War veterans with any neurological symptoms by exposures

	Gulf War veterans with any neurological symptoms						
Gulf War exposure	**N**	**n**	**%**	**OR**	**Adj OR**	**95% CI**	**P value**
Immunisations							
None	119	53	45	1.0	1.0	-	-
Any	956	495	52	1.3	1.3	0.9-2.0	0.169
1-4	267	118	44	1.1	1.0	0.6-1.6	0.945
5-9	564	307	54	1.6	1.5	1.0-2.3	0.060
10 or more	125	70	56	1.6	1.6	0.9-2.7	0.105
Dose response in those ≥ 1	-	-	-	1.05	1.05	1.01-110	0.019
Don't know	342	202	59	1.8	1.8	1.0-2.5	0.046
Clustering - none	961	490	51	1.0	1.0	-	-
Clustering – any	151	81	54	1.1	1.2	1.0-2.7	0.065
Pyridostigmine bromide							
None	371	170	46	1.0	1.0	-	-
Any	727	396	54	1.4	1.3	1.0-1.7	0.100
1 – 80 tablets taken	151	71	47	1.0	1.0	0.7-1.5	
81 – 180 tablets taken	156	93	60	1.7	1.4	0.9-2.2	
>180 tablets taken	148	86	58	1.6	1.3	0.9-2.1	
Dose response in those ≥ 1	-	-	-	1.2	1.1	1.0-1.3	0.088
Don't know	318	183	58	1.6	1.4	1.0-2.0	0.031
Antimalarials							
None	283	121	43	1.0	1.0	-	-
Yes	586	322	55	1.6	1.4	1.1-2.0	0.019
Don't know	543	303	56	1.7	1.4	1.0-1.9	0.031
Anti-biological warfare tablets							
None	540	237	44	1.0	1.0	-	-
Yes	80	50	62	2.1	1.8	1.1-2.9	0.027
Don't know	793	461	58	1.8	1.6	1.3-2.1	<0.001
Solvents							

	Gulf War veterans with any neurological symptoms						
Gulf War exposure	**N**	**n**	**%**	**OR**	**Adj OR**	**95% CI**	**P value**
No	303	126	42	1.0	1.0	-	-
Yes	1110	624	56	1.8	1.6	1.1-2.2	0.006
Pesticides / insecticides							
No	1027	496	48	1.0	1.0	-	-
Yes	380	249	66	2.0	1.9	1.4-2.4	<0.001
Repellents							
No	1049	532	51	1.0	1.0	-	-
Yes	363	215	59	1.4	1.5	1.1-1.9	0.005

The pattern of the relation between total number of neuropathic symptoms and exposures was similar. These symptoms were associated with several exposures examined in this subanalysis, including anti-biological warfare tablets, solvents, pesticides/insecticides and repellents, but not with some other exposures such as having received any immunisations or clustering of immunisations (Table 13.7). The total number of neuropathic symptoms was also associated with pyridostigmine bromide and anti-biological warfare tablets in those subjects who reported that they did not know whether they had taken pyridostigmine bromide or anti-biological warfare tablets. Increasing number of immunisations received and increasing number of pyridostigmine bromide tablets was associated with total number of neurological symptoms in a dose response relationship. The dose response relationship for immunisations is of further interest. There is a decrease in the risk (adjusted odds ratio 0.8) for those who received 1-4 immunisations, and the risk of immunisations for total number of neuropathic symptoms does not increase until receipt of 10 or more immunisations (adjusted OR 1.5).

Table 13.7 Subanalysis of total number of neuropathic symptoms in Gulf War veterans by exposures

Gulf War exposure	Total number of neuropathic symptoms						
	N	**Mean**	**(SD)**	**Ratio**	**Adj Ratio**	**95% CI**	**P value**
Immunisations							
None	119	1.5	(2.6)	1.0	1.0	-	-
Any	956	1.5	(2.4)	1.0	1.1	0.8-1.5	0.571
1-4	267	1.1	(1.8)	0.7	0.8	0.6-1.1	
5-9	564	1.6	(2.4)	1.1	1.1	0.8-1.5	
10 or more	125	2.2	(3.1)	1.5	1.5	1.1-2.3	
Dose response in those $\geq$1	-	-	-	1.08	1.07	1.04-1.10	<0.001
Don't know	342	2.0	(2.8)	1.4	1.3	0.9-1.8	0.115
Clustering - none	961	1.5	(2.4)	1.0	1.0	-	-
Clustering – any	151	1.7	(2.7)	1.1	1.1	0.8-1.5	0.407
Pyridostigmine bromide							
None	371	1.2	(1.8)	1.0	1.0	-	-
Any	727	1.8	(2.6)	1.5	1.5	1.2-1.8	<0.001
1 – 80 tablets taken	151	1.5	(2.5)	1.3	1.4	1.0-1.8	
81 – 180 tablets taken	156	2.1	(3.0)	1.8	1.6	1.2-2.1	
>180 tablets taken	148	2.0	(2.7)	1.7	1.6	1.2-2.1	
Dose response in those $\geq$1	-	-	-	1.2	1.2	1.1-1.3	0.001
Don't know	318	2.0	(2.8)	1.7	1.6	1.3-2.0	<0.001
Antimalarials							
None	283	1.2	(2.2)	1.0	1.0	-	-
Yes	586	1.8	(2.6)	1.4	1.3	1.0-1.6	0.065
Don't know	543	1.7	(2.5)	1.4	1.1	0.9-1.4	0.325
Anti-biological warfare tablets							
None	540	1.2	(2.1)	1.0	1.0	-	-
Yes	80	2.6	(3.4)	2.1	1.8	1.3-2.5	<0.001
Don't know	793	1.9	(2.6)	1.5	1.4	1.2-1.7	<0.001
Solvents							
No	303	1.0	(1.7)	1.0	1.0	-	-
Yes	1110	1.8	(2.7)	1.9	1.8	1.4-2.2	<0.001
Pesticides / insecticides							
No	1027	1.3	(2.2)	1.0	1.0	-	-
Yes	380	2.5	(3.1)	1.9	1.7	1.5-2.0	<0.001
Repellents							
No	1049	1.6	(2.4)	1.0	1.0	-	-
Yes	363	2.0	(2.8)	1.3	1.2	1.0-1.5	0.014

The neuropathy impairment score was not associated with any of the exposure metrics (Table 13.8). The only weak association found was for those people who didn't know whether they had received antimalarials.

Table 13.8 Subanalysis of neuropathy impairment score of Gulf War veterans by exposures

Gulf War exposure	Neuropathy impairment score (sum of left and right)						
	N	**Mean**	**(SD)**	**Ratio**	**Adj Ratio**	**95% CI**	**P value**
Immunisations							
None	113	1.8	(4.2)	1.0	1.0	-	-
Any	914	1.9	(4.0)	1.0	1.0	0.6-1.6	0.984
1 - 4	253	2.0	(3.9)	1.1	1.1	0.7-1.8	
5 - 9	536	1.8	(3.9)	1.0	1.0	0.6-1.5	
10 or more	125	1.9	(4.6)	1.0	0.9	0.5-1.6	
Dose response in those $\geq$1	-	-	-	0.97	0.95	0.90-1.00	0.036
Don't know	317	2.5	(2.5)	1.3	1.3	0.8-2.0	0.359
Clustering - none	917	1.4	(4.0)	1.0	1.0	-	-
Clustering – any	146	1.8	(4.2)	1.0	1.0	0.7-1.6	0.845
Pyridostigmine bromide							
None	342	2.1	(5.0)	1.0	1.0	-	-
Any	697	1.8	(3.9)	0.9	0.8	0.6-1.1	0.216
1 – 80 tablets taken	150	1.6	(3.4)	0.7	0.8	0.5-1.2	
81 – 180 tablets taken	145	2.4	(4.8)	1.1	0.9	0.6-1.4	
>180 tablets taken	146	1.7	(3.7)	0.8	0.8	0.5-1.2	
Dose response in those $\geq$1	-	-	-	1.0	1.0	0.8-1.1	0.522
Don't know	303	2.3	(4.4)	1.1	1.1	0.8-1.5	0.703
Antimalarials							
None	266	1.6	(3.3)	1.0	1.0	-	-
Yes	559	1.8	(3.9)	1.1	1.0	0.7-1.4	0.972
Don't know	514	2.5	(5.1)	1.6	1.4	1.0-2.0	0.046
Anti-biological warfare tablets							
None	506	2.0	(4.4)	1.0	1.0	-	-
Yes	80	2.1	(5.0)	1.1	0.9	0.5-1.5	0.672
Don't know	754	2.0	(4.2)	1.0	1.0	0.7-1.2	0.691
Solvents							
No	276	1.7	(3.6)	1.0	1.0	-	-
Yes	1063	2.1	(4.5)	1.2	1.1	0.8-1.5	0.682
Pesticides / insecticides							
No	973	1.9	(3.8)	1.0	1.0	-	-
Yes	359	2.4	(5.4)	1.3	1.1	0.8-1.4	0.597
Repellents							
No	996	2.0	(4.3)	1.0	1.0	-	-
Yes	341	2.1	(4.3	1.1	1.1	0.8-1.4	0.527

13.5 Discussion

In this chapter we compared neurological health outcomes in Gulf War veterans and the comparison group according to definitions that utilised various combinations of neuropathic symptoms and neurological physical examination signs.

The main findings are that Gulf War veterans reported more individual neuropathic symptoms than the comparison group and more neuropathic symptoms in total. Gulf War veterans also had more symptoms and signs suggestive of a neuropathic disorder. There was no difference in the neuropathy impairment score, which is based on physical signs alone. The combinations of neuropathic symptoms and physical signs that were used in the operational definitions developed for the purposes of our study suggests that more Gulf War veterans than comparison group subjects have neurological symptoms and signs consistent with myopathy, a central nervous system disorder and epilepsy, but not with disorders of peripheral motor neurones or their axons. However, the numbers of operational cases were very small, giving the study limited power to identify associations with Gulf War service.

The reporting of any neuropathic symptoms and the total number of neuropathic symptoms were associated with various exposures that occurred in the Gulf War, including immunisations and pyridostigmine bromide tablets in a dose response relationship and some other exposures including antimalarials, anti-biological warfare tablets, solvents, repellents and pesticides/insecticides. The neuropathy impairment score was not associated with any exposures. The reporting of any neuropathic symptoms and the total number of neuropathic symptoms were also associated with various exposures in those who reported that they did not know whether they had received medication such as pyridostigmine bromide, antimalarials or anti-biological warfare agents and it is possible, considering the feedback received from participants during the data follow-up and checking process by the study team, that these individuals may have received such medication but were hesitant about committing to a response when they were not sure.

The neuropathic symptoms reported in this study can be reported by people with peripheral neuropathy but are also similar to psychological symptoms that may be reported in people exposed to psychological stresses or with anxiety or depressive disorders.

The combinations of neuropathic symptoms and physical signs used in the definition of a neuropathic disorder in our study are consistent with those of a peripheral neuropathy. Peripheral neuropathy has been the subject of epidemiological study in previous Gulf War veteran health research, with Cherry *et al*[157] finding that more Gulf War veterans reported symptoms suggestive of peripheral neuropathy than the comparison group (12.5% vs 6.8%). Our association was not as strong as this.

There could be a number of causes for the excess we found in central nervous system disorder, as defined in our study. Multiple sclerosis would be one cause of a central nervous system disorder in the age range of our study participants, although stroke could also be a cause of a central nervous system disorder defined in this way. Such disorders have not been the subject of previous study by other Gulf War health research groups.

The combination of neuropathic symptoms and physical signs used in the definition of a disorder of peripheral motor neurones or their axons in our study can be consistent with those of motor neurone disease. Although the results have not yet been published in the peer reviewed scientific literature, a recent study in the US has been reported as finding that of 700 000 Gulf War veterans, 40 had motor neurone disease (known in the United States as

amyotrophic lateral sclerosis or Lou Gehrig's disease), a case rate of 6.7 per million. Of 1.8 million US veterans in the same period who did not deploy to the Gulf War, 67 developed motor neurone disease, a case rate of 3.5 per million[233] (http://www.gulflink.osd.mil/news/na als remarks 10 dec01.html). We found no excess disorders of peripheral motor neurones to support the US finding.

There is also some evidence from previous studies to suggest that other adverse neurological health outcomes are more common in Gulf War veterans, and there is inconclusive evidence to suggest that these may be related to exposures that occurred in the Gulf. Adverse neurological outcomes have been associated with exposure to pesticides[28, 29, 31, 94] although this has not been consistently reported.[33] It has also been postulated that organophosphate insecticides, or possible nerve agent exposure, have been associated with chronic neuropathic impairment, and that combinations of possible chemical exposures may have worked synergistically to produce an effect.[31, 158] The findings of a more detailed evaluation of neurological evaluation function in a subset of Gulf War veterans[170] have been non-specific, although studies of basal ganglia function[232] have suggested that central neurotransmitter production may have been affected in a lateralised pattern. The evidence is not conclusive in this field of study, and there have been methodological problems acknowledged in these studies, including the lack of a comparison group.[25]

Although the definitions that were used to compare the study groups were developed for this study in consultation with a neurologist, there are some limitations to our findings for neurological health outcomes. The neuropathic symptom questionnaire was not a validated questionnaire, and did not include qualifying questions around the duration of symptoms or questions that would have assisted in identifying those whose reported symptoms were due to a medical condition that was not neurological. For example, difficulty getting up from a chair or difficulty unscrewing jars could be related to arthritis. Although the neuropathic symptom questionnaire and the definitions have face validity, they have not been validated in clinical practice.

Neurological signs may not always be present even when symptoms or a clinical history suggests that a neurological disorder is present. As discussed in the General Health chapter of this report, neuropsychological or neurocognitive symptoms were the most commonly reported symptoms by both groups, and were reported by a significantly greater proportion of Gulf War veterans than the comparison group. Impaired neurocognitive function may be an early indicator of impaired central nervous system function, even before physical examination signs are evident.

The process of defining neurological outcomes used in our study was not intended to be diagnostic. The diagnostic process requires additional history, physical examination and quantitative investigations such as nerve conduction studies, other quantitative neurological tests, diagnostic imaging studies or neurocognitive function testing that were not able to be included in our study.

The general evaluation of participation bias in our study (see Recruitment chapter) has shown that effects on odds ratios are likely to be small and therefore participation bias is unlikely to explain the differences we found in neurological health status between the Gulf War veterans and the comparison group. More directly, application of the non-participation imputation procedure detailed in the Recruitment chapter to the examination of differences in prevalence of any neuropathic symptom between Gulf War veterans and comparison group subjects revealed only minor effects of nonparticipation. The mean of the age, rank and service-adjusted odds ratios from the imputation procedure correcting for non-participation was 1.36,

which is only marginally lower than the corresponding odds ratio of 1.42 among participants. The findings for other neurological outcomes would probably be similar in effect. However, some caution should applied to the interpretation of these analyses as they are based on statistical models with underlying assumptions and the representativeness of the SF-12 data from the telephone-questionnaire participants (see chapter 6 for more detail).

Information bias is another form of bias that may have affected the results of this study, if Gulf War veterans were more susceptible to influences from avenues such as the media on self-reporting of neuropathic symptoms or neurological disorders. This source of bias would not have affected the objective measures of physical health used to assess the health status of both groups such as the neurological examination, and thus should not have affected the neurological health outcomes that were defined according to combinations of symptoms and physical signs. It is interesting to note that associations with the exposure metrics were only found for those definitions made up of symptoms, rather than physical signs.

We controlled for a core set of confounders as well as confounders such as diabetes and alcohol use that are known to increase the risk of neurological disease, but it is possible that other confounders, not identified, may have had an impact on the results.

Although there are some limitations to the approach used in our study, a strength of the study is the use of a comparison group to whom the same definitions were applied in the same manner. Many of the conclusions of other epidemiological studies of Gulf War veterans' neurological health have been based solely on self-reported findings. The use of a neurological physical examination in our study has increased the objectivity of this study, but there are limited neurological health data from other Gulf War veteran cross-sectional studies with which to compare our results.

13.5.1 Summary of findings

In summary, and in answer to the research questions, a greater proportion of Gulf War veterans report neuropathic symptoms than the comparison group. Gulf War veterans also have more neuropathic symptoms and physical signs indicative of a neuropathic disorder than the comparison group according to the operational definitions used in this study.

Gulf War veterans have more neurological symptoms or physical signs indicative of adverse neurological health outcomes such as myopathy, a central nervous system disorder and epilepsy than the comparison group, although the difference is of statistical significance only for central nervous system disorder.

Gulf War veterans do not have more neurological symptoms or physical signs indicative of disorders of peripheral motor neurones or their axons according to the operational definition used in this study. The numbers of operational cases were very small, giving the study limited power to identify associations with Gulf War service.

Reporting of 'any' neuropathic symptoms was associated with several exposures that occurred in the Gulf War. These include antimalarials, anti-biological warfare tablets, solvents, pesticides/insecticides and repellents. There was also a weak dose response relationship found for the number of immunisations and number of pyridostigmine bromide tablets.

The total number of neuropathic symptoms was associated with anti-biological warfare tablets, solvents, pesticides/insecticides and repellents, but not with some other exposures such as having received any immunisations or clustering of immunisations. Increasing

number of immunisations received and increasing number of pyridostigmine bromide tablets were associated with the total number of neurological symptoms in a dose response relationship.

The neuropathy impairment score, based on physical neurological examination findings only, and not on neuropathic symptoms, was not associated with any of the Gulf War exposures.

The analysis of adverse neurological health outcomes presented in this chapter is based on combinations of symptoms and physical signs, and if these findings were to be investigated further, additional data would need to be collected, such as nerve conduction studies. Further evaluation would be required to determine whether the combinations of symptoms and physical signs are due to pathology affecting the peripheral or central nervous systems, and whether this can be verified by objective diagnosis and investigations.

14. Chronic fatigue syndrome

14.1 Aim

The aim of this analysis is to investigate whether male Australian Defence Force personnel who served in the Gulf War have a higher rate of chronic fatigue syndrome than the comparison group; and, if so, whether this is associated with exposures and experiences that occurred in the Gulf?

14.2 Research questions

1. Do Australian Gulf War veterans have significantly more chronic fatigue syndrome than the comparison group?

2. Is chronic fatigue syndrome in Gulf War veterans associated with exposure to chemical or environmental agents, infectious agents or the use of prophylactic medications or immunisations?

3. Does the immunological profile of Gulf War veterans with chronic fatigue syndrome differ from that of comparison group subjects with chronic fatigue syndrome?

14.3 Definitions and classification of fatigue

The methodological approach to the assessment of chronic fatigue in this study was based on the criteria for the epidemiological investigation of chronic fatigue syndrome as recommended by Fukuda *et al*.[305] The assessment of fatigue and chronic fatigue outcomes in this study was based on:

- a HSA doctor's standardised interview of the participant to establish a history of fatigue and chronic fatigue and to assess the severity of the fatigue and the presence of associated symptoms.
- a medical evaluation of the history, physical examination, psychological assessment and laboratory investigations on all cases of chronic fatigue to determine whether there was a medical or psychological condition that may explain the chronic fatigue, with the doctor undertaking this evaluation blinded to the Gulf War status of the subjects,
- other exposure and health outcomes data for the purposes of subgrouping cases of chronic fatigue syndrome.

14.3.1 Definitions of fatigue and chronic fatigue syndrome

For the purpose of this study, the following definitions, based on those developed by Fukuda *et al*,[305] were used to define various states of fatigue and chronic fatigue syndrome. By definition, all subjects who met the following criteria would have experienced extreme tiredness or fatigue at some time in the past 12 months.

Fatigue

Participants were defined as having fatigue if, in the past 12 months, the participant had experienced extreme tiredness or fatigue following his normal activities.

Prolonged fatigue
Participants were defined as having prolonged fatigue if, in the past 12 months, the participant had felt extremely tired or fatigued following his normal activities every day, or almost every day, for one month or longer.

Chronic fatigue
Participants were defined as having chronic fatigue if the participant had had a period(s) of extreme tiredness or fatigue that had been persistent, relapsing or recurring for a total duration of at least 6 months or more since it first began.

Medically explained chronic fatigue and medically unexplained chronic fatigue
Participants were defined as having:

- medically explained chronic fatigue if the participant had chronic fatigue that could be explained by a medical or psychological condition according to the medical evaluation.
- medically unexplained chronic fatigue if the participant had chronic fatigue that had not been explained by a medical or psychological condition according to the medical evaluation.

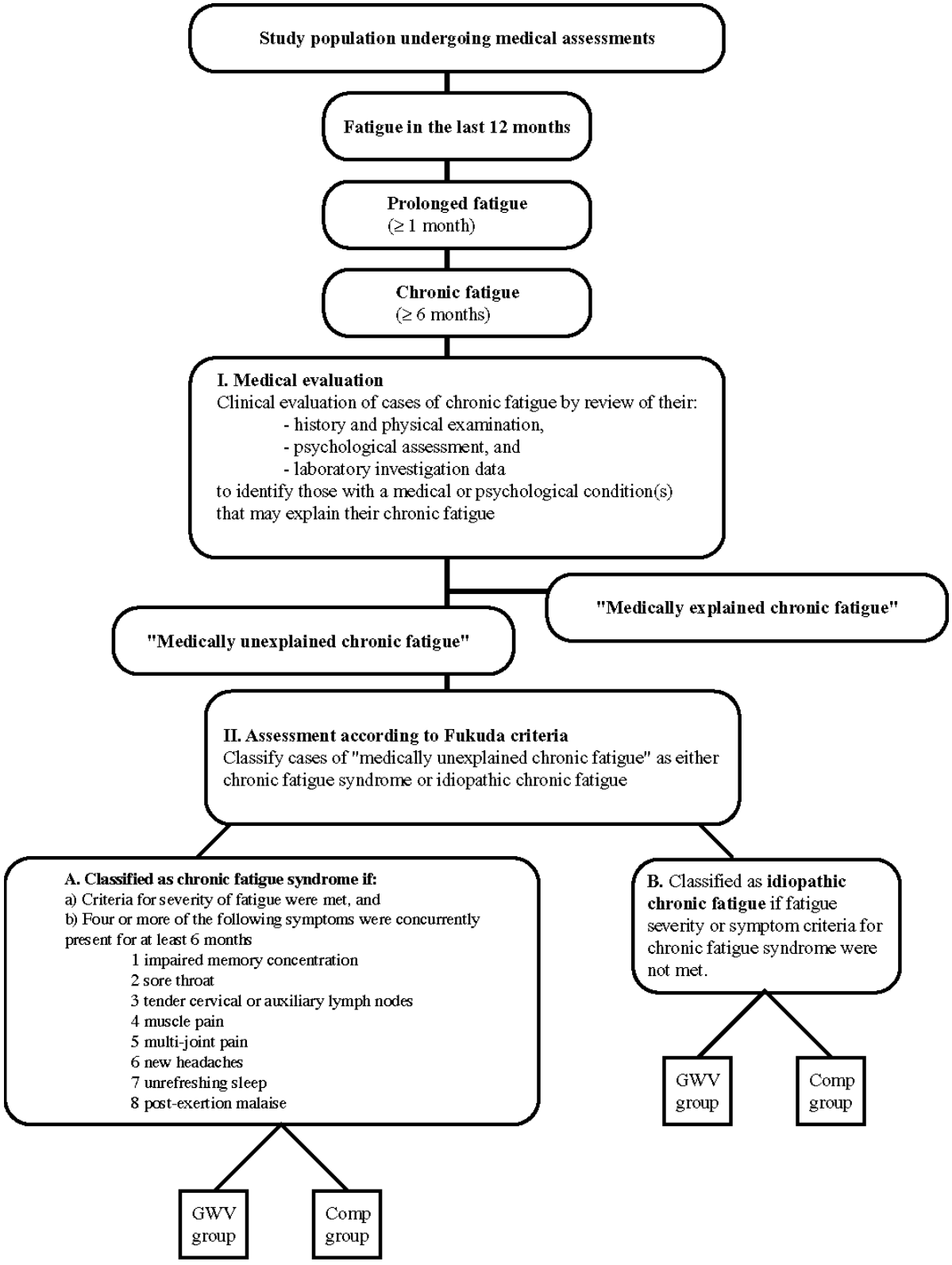
Chronic fatigue syndrome
Participants were defined as having chronic fatigue syndrome if the participant had medically unexplained chronic fatigue that was of new or definite onset (had not been lifelong), and

- the participant met the criteria for the severity of fatigue, that is the feeling of extreme tiredness or fatigue was not substantially alleviated by rest (they had some recovery, no recovery or their fatigue was worse following rest, sleep or relaxation), and resulted in substantial reduction in previous levels of occupational, educational, social or personal activities (they were able to do <75% of their normal activities during these periods of extreme tiredness or fatigue), and
- the participant had experienced at least four or more of the following symptoms, which had not predated the fatigue, and each of which had been present for at least a total of 6 months, and the four or more symptoms had been present concurrently for at least 6 consecutive months:
  - Self-reported impairment in short-term memory or concentration
  - Sore throat
  - Tender cervical or axillary lymph nodes
  - Muscle pain
  - Multi-joint pain without joint swelling or redness
  - Headaches of a new type, pattern or severity
  - Unrefreshing sleep
  - Post-exertional malaise lasting more than 24 hours.

Idiopathic chronic fatigue
Participants were defined as having idiopathic chronic fatigue if the participant had medically unexplained chronic fatigue that did not meet the severity or symptom criteria for chronic fatigue syndrome.

The steps in the process of defining cases of chronic fatigue syndrome in this study, based on the Fukuda *et al* criteria,[305] are summarised in Figure 14.1. These steps in the process were undertaken without knowing the Gulf War status, which was revealed at the end of the process.

Figure 14.1 Process for defining cases of chronic fatigue syndrome



14.4 Results

14.4.1 Fatigue and chronic fatigue syndrome

One female study participant was identified as having chronic fatigue and this is reported in the chapter 15. The following results refer to males only.

Table 14.1 shows that Gulf War veterans reported all fatigue-related health outcomes more commonly than the comparison group. Gulf War veterans reported more extreme tiredness or fatigue at any time in the last 12 months, more prolonged fatigue, and were identified as having more chronic fatigue, than the comparison group. The proportion of subjects reporting an increasing duration of fatigue decreased steadily in both groups. The risk of Gulf War veterans having chronic fatigue, which was not considered to be explained by a medical or psychological condition, was more than twice that of the comparison group. The risk of Gulf War veterans having chronic fatigue syndrome according to the study criteria was five times that of the comparison group. The odds ratios increased with increasing refinement and clinical evaluation of the nature of the fatigue. The numbers of cases of chronic fatigue syndrome were small, especially in the comparison group, and need to be interpreted with caution.

Table 14.1 Prevalence and ORs of fatigue, prolonged fatigue and chronic fatigue (medically explained and unexplained), idiopathic chronic fatigue and chronic fatigue syndrome

	GWV N=1382*		Comp grp N=1377*		Crude OR	Adj OR†	95% CI	P value
	n	%	n	%				
Fatigue in the last 12 months	262	19.0	159	11.5	1.8	1.7	1.4-2.2	<0.001
Prolonged fatigue (≥1 month)	132	9.6	74	5.4	1.9	1.8	1.3-2.5	<0.001
Chronic fatigue (≥6 months)	109	7.9	58	4.2	2.0	1.9	1.4-2.7	<0.001
Unexplained chronic fatigue*	92	6.7	40	2.9	2.4	2.3	1.6-3.5	<0.001
Idiopathic chronic fatigue	77	5.6	37	2.7	2.1	2.1	1.4-3.2	<0.001
Chronic fatigue syndrome	11	0.8	2	0.1	5.5	5.0‡	1.1-47.4	0.036

* There were minor variations in the 'n' for each fatigue-related outcome because small numbers of missing variables meant that the outcome could not be computed (4 Gulf War and 1 comparison group subject had missing values or 'don't know' information for one or more of the severity or symptom criteria for assessing chronic fatigue syndrome) or data for computation of adjusted odds ratios were not available on up to 30 participants.
† Odds ratios were adjusted for age (<20, 20-<25, 25-<35, ≥35 years), service type, rank, education, marital status, smoking (current, former, ever) and alcohol (AUDIT score >8)
‡ Odds ratio obtained by exact logistic regression adjusting for age (<25,≥25 years), service type and rank

One hundred and sixty-seven male subjects (109 Gulf War veterans and 58 comparison group subjects) were identified as having chronic fatigue (Table 14.1). A medical or psychological condition that could have explained the chronic fatigue, after a blinded medical review, was identified in 35 subjects (17 Gulf War and 18 comparison group subjects), and these are summarised in Table 14.2.

There were a wide variety of medical or psychological conditions that were assessed as explaining the chronic fatigue. The number of subjects with each condition was small.

Table 14.2 Medical or psychological conditions assessed as explaining the chronic fatigue

Medical or psychological conditions	n
Alcohol or other substance abuse	
Alcohol abuse*	4
Active medical conditions†	
Cancer	5
Neurological conditions	2
Gastrointestinal conditions	1
Endocrine condition	1
Respiratory condition, including uncontrolled asthma (• 30 attacks in the last 12 months)	3
Psychological conditions (with no active medical condition)	
Bipolar I disorder, Manic	7
Sleep apnoea or narcolepsy	
Self-reported sleep apnoea or narcolepsy‡	8
Others	
Physical labour/exertion or lifestyle changes	4

* Alcohol abuse had been diagnosed by the CIDI and had had an onset within 2 years before the onset of the chronic fatigue and at any time afterward

† Of those with an active medical condition assessed as explaining the fatigue, one subject also had sleep apnoea, and two other subjects also had Bipolar I disorder, Manic.

‡ Self-reported narcolepsy or sleep apnoea was considered as a possible explanation for the chronic fatigue if it was rated as a possible or probable diagnosis by a HSA doctor and been assessed as having the potential to explain the chronic fatigue from a chronological perspective

Of the eleven Gulf War veterans assessed as having chronic fatigue syndrome, ten were Navy and one was Army. Of the two comparison group participants assessed as having chronic fatigue syndrome, one was from the Navy and one was from the Army.

14.4.1.1 Fitness test results

The fitness test was used as an objective measure of fitness and fatigability. The results for the two study groups overall are presented in the General Health chapter. Of the 11 Gulf War veterans with chronic fatigue syndrome, seven were assessed by a HSA doctor as fit to perform the fitness test, and all completed the 3-minute test. Fatigue was given as a reason for not performing the fitness test in one Gulf War veteran, and for the others the reasons related to medical or musculoskeletal problems. Three of these Gulf War veterans had mean recovery heart rates in the 'low' fitness category and four had mean recovery heart rates in the 'medium' fitness category. One of the two comparison group subjects with chronic fatigue syndrome was assessed as fit to perform the fitness test, and a musculoskeletal problem was given by the other as a reason for not performing the test. The comparison group subject who did perform the test had a mean recovery heart rate in the 'medium' fitness category. These numbers are small and should be interpreted with caution.

14.4.2 Immunological profile of cases of chronic fatigue syndrome

The immunological profile of Gulf War veteran and comparison group cases of chronic fatigue syndrome was compared using lymphocyte subsets. Table 14.3 shows the mean and standard deviations of lymphocyte subset expressed as absolute cell counts and as a

percentage of the total lymphocyte count (lymphocyte %). The mean cell counts of white blood cell, lymphocytes and lymphocyte subsets were similar for Gulf War veterans and the comparison group, and were within the reference intervals for both study groups, except for CD16+/CD56+CD3- which was very slightly below the reference interval in both study groups. When expressed as a percentage of total lymphocytes, all mean lymphocyte percentages were similar in Gulf War veterans and the comparison group. The mean lymphocyte percentages were all also within their reference intervals, except for CD19, a B cell marker, which was slightly elevated in both study groups.

Table 14.3 Mean and standard deviation (SD) of lymphocyte subset test results

	Gulf War veterans (N=11)		**Comp grp (N=2)**	
Parameter	**mean**	**(SD)**	**mean**	**(SD)**
Cell counts				
White cell count (4.0-11.0 x 10^9/L)	7.2	(1.8)	6.7	(0.7)
Lymphocyte count (1.0-4.0 x 10^9/L)	2.2	(0.6)	2.1	(0.2)
T cell markers				
CD3 (0.66-3.22 x 10^9/L)	1.7	(0.4)	1.6	(0.2)
CD4+CD3+ (0.41-2.21 x 10^9/L)	1.1	(0.3)	1.0	(0.01)
CD8+CD3+ (0.17-1.33 x 10^9/L)	0.5	(0.2)	0.5	(0.2)
B cell markers				
CD19 (0.30-0.53 x 10^9/L)	0.4	(0.2)	0.4	(0.1)
Natural Killer Cell markers				
CD16+CD3-, x 10^9/L*	6.1	(3.0)	4.0	(0.0)
CD56+CD3-, x 10^9/L*	5.0	(2.9)	4.0	(1.4)
CD16+/CD56+CD3- (0.15-0.46 x 10^9/L)	0.1	(0.08)	0.1	(0.02)
% lymphocytes				
T cell markers				
CD3 (44-90%)	74.6	(7.5)	77.0	(1.4)
CD4+CD3+ (27-63%)	48.1	(8.5)	50.5	(5.0)
CD8+CD3+ (11-38%)	23.8	(5.6)	24.0	(8.5)
B cell markers				
CD19 (2-15%)	16.0	(6.6)	17.5	(0.7)
Natural Killer Cell markers				
CD16+CD3-, x 10^9/L*	6.1	(3.0)	4.0	(0.0)
CD56+CD3-, x 10^9/L*	5.0	(2.9)	4.0	(1.4)
CD16+/CD56+CD3- (1-13%)	6.5	(2.8)	4.0	(1.4)

*IMVS does not report a reference interval for these lymphocyte subsets

Table 14.4 shows the prevalences of lymphocyte subset cell counts in relation to the laboratory reference intervals. Almost half of the Gulf War veteran group cases of chronic fatigue syndrome had CD19 (B cell marker) and CD16+/CD56+CD3- (Natural Killer Cell

marker) cell counts lower than the reference intervals, whilst 2 cases had a CD19 count higher than the reference interval. Both comparison group cases of chronic fatigue syndrome had CD16+/CD56+CD3- marker cell counts lower than the reference interval. The white cell counts, lymphocyte counts and T cell marker counts of both study group cases of Gulf War veterans and comparison group cases of chronic fatigue syndrome were within the reference intervals.

Table 14.4 Prevalence for lymphocyte subset test results (cell counts) in chronic fatigue syndrome cases in relation to laboratory reference intervals

	Gulf War veterans (N=11)		Comparison group (N=2)	
Parameter (cell counts)	**n**	**(%)**	**n**	**(%)**
White cell count within ref interval (4.0-11.0 x 10^9/L)	11	(100.0)	2	(100.0)
Lymphocyte count within ref interval (1.0-4.0 x 10^9/L)	11	(100.0)	2	(100.0)
T cell markers				
CD3 within ref interval (0.66-3.22 x 10^9/L)	11	(100.0)	2	(100.0)
CD4+CD3+ within ref interval (0.41-2.21 x 10^9/L)	11	(100.0)	2	(100.0)
CD8+CD3+ within ref interval (0.17-1.33 x 10^9/L)	11	(100.0)	2	(100.0)
B cell marker				
CD19 within ref interval (0.30-0.53 x 10^9/L)	4	(36.4)	2	(100.0)
<0.30-0.53 x 10^9/L	5	(45.5)	0	(0.0)
>0.30-0.53 x 10^9/L	2	(18.2)	0	(0.0)
Natural Killer Cell marker				
CD16+/CD56+CD3- within ref interval (0.15-0.46 x 10^9/L)	6	(54.5)	0	(0.0)
< 0.15-0.46 x 10^9/L	5	(45.5)	2	(100.0)

14.4.3 Gulf War veteran group subanalysis

The small number of cases of chronic fatigue syndrome in Gulf War veterans was considered too small to undertake further subanalysis in relation to exposures and experiences that occurred in the Gulf War.

14.5 Discussion

This analysis has compared fatigue-related health outcomes between the Gulf War veterans and the comparison group. The main finding is that Gulf War veterans report more fatigue at all duration and levels of fatigue considered in this study. Gulf War veterans have been assessed as having more extreme tiredness or fatigue following normal activities in the past 12 months, more prolonged fatigue, more chronic fatigue, more chronic fatigue which had not been explained by a medical or psychological condition according to the medical evaluation, and more chronic fatigue syndrome than the comparison group. The number of subjects assessed as having chronic fatigue syndrome is small, and needs to be interpreted with caution. There are some differences between Gulf War veterans and the comparison group, and for both study groups, in relation to laboratory reference intervals for two of the lymphocyte subsets that were used to assess immunological function in this study; but the

clinical significance of these is uncertain and further interpretation is limited because of the small numbers involved.

Fatigue in the past month was one of the most common symptoms that was self-reported by both Gulf War veteran (66%) and comparison group (56%) subjects in the postal questionnaire in our study. These proportions are considerably higher than those who reported that they had experienced extreme tiredness or fatigue following their normal activities in the past 12 months when interviewed by a HSA doctor (19.0% vs 11.5%). As reported in the General Health chapter, a similar proportion of Gulf War veterans and comparison group subjects self-reported that they have had chronic fatigue syndrome, that had been diagnosed in 1991 or later {13 (1%) vs 17 (1%)}; and self-reported that they have had chronic fatigue syndrome, that had been diagnosed in 1991 or later, and was assessed as a possible or probable diagnosis by a HSA doctor {10 (1%) vs 9 (1%)}. Unlike the chronic fatigue syndrome results presented in this chapter where, by definition, extreme tiredness or fatigue must have been present at some time in the last 12 months, the self-reported chronic fatigue syndrome condition may not have been current or have been experienced in the past 12 months.

The small number of subjects with chronic fatigue syndrome, according to the study definition, in both study groups limited the subgrouping of cases according to parameters such as comorbid conditions, duration of fatigue, and current level of physical functioning. We did investigate the immunological profile of Gulf War veterans and comparison group subjects using lymphocyte subsets. The mean CD19 lymphocyte subset for both study groups were slightly higher than the IMVS reference interval, and the mean CD16+/CD56+CD3- interval for both groups was very slightly lower than the IMVS reference interval. Almost half the Gulf War veteran cases of chronic fatigue syndrome had CD19, a B cell lymphocyte marker, test results that were lower than the laboratory reference interval. Almost half the Gulf War veteran cases and both the comparison group cases of chronic fatigue syndrome had CD16+/CD56+CD3-, a Natural Killer cell marker, test results that were lower than the laboratory reference interval. The white cell, total lymphocyte and T cell lymphocyte subset parameters of Gulf War veterans and comparison group were similar. Both the numbers of subjects assessed as having chronic fatigue syndrome and the number of test results outside the reference interval are small, and the significance of these findings is uncertain.

The reference intervals for lymphocyte have a number of limitations, and are being reviewed by IMVS. The reference intervals for lymphocyte subpopulations were established through testing of between 20-120 people for whom a specific test relevant to the diagnosis of arthritis had been ordered by their doctors. Lymphocyte subpopulation levels can vary on a day to day basis and diurnally. Large variations in the levels of lymphocyte parameters can be caused by external factors such as sleep, intercurrent viral illness, exercise and depression. Thus, shifts in the levels of lymphocyte subpopulations are of most use in monitoring individuals over time or if the changes are marked. The interpretation of small changes in lymphocyte levels, and interpretations against reference intervals, is considered to be more difficult.

Fatigue as a self-reported symptom and chronic fatigue or chronic fatigue syndrome as a medical condition has been reported by several of the overseas studies. The approach to defining cases of chronic fatigue syndrome and the other states of fatigue that was used in our study, was based on the Fukuda *et al* criteria[305] which were developed by an International Chronic Fatigue Syndrome Study Group in recognition of the need for a comprehensive and

systematic approach to the definition and study of chronic fatigue syndrome. Other Gulf War health epidemiological research groups[16, 73] and recent clinical practice guidelines[391] have based their definitions of chronic fatigue syndrome on these criteria. These clinical practice guidelines have also discussed managing patients with chronic fatigue syndrome.

Previous studies have found that reports of fatigue-related symptoms are common in Gulf War veterans. Symptoms of fatigue, tiredness, lacking in energy, needing to rest more or feeling unusually sleepy/drowsy have been reported as symptoms by up to 50% of Gulf War veterans in several studies[20, 21, 160] and more frequently than by the non-Gulf comparison groups. The proportions of Gulf War veterans (66%) and comparison group (56%) subjects self-reporting fatigue as a symptom in our study is greater. Extreme fatigue every day, or almost every day, was reported by 23% of Iowa Gulf War veterans and 9% of non-Gulf veterans,[160] and these results are similar to those of our study (19.0% vs 11.5%). Fatigue lasting 24 hours was reported by 20% of US Gulf War veterans.[20] In UK Gulf War veterans, feelings of tiredness were the most troublesome symptoms, with the highest mean symptom scores, in both the Gulf War veteran and comparison groups, although as with all other symptoms the score was higher in the Gulf War veteran group.[157] Being "overly tired/lack of energy" was reported by 22.2% of a New England cohort of Gulf War veterans, but by 78.2% of a high symptom group and by 30.7% of a moderate symptom group within this cohort.[159] Thus, there is considerable variation in the proportions reporting fatigue-related symptoms in these overseas studies, but the questions used to assess these symptoms were also different.

Previous overseas studies have also found that fatigue-related medical conditions are more common in Gulf War veterans. Chronic fatigue syndrome or myalgic encephalitis was self-reported as a medical condition by 3.3% of UK Gulf War veterans.[21] Gulf War veterans were more likely than the Bosnia and Era cohort to have substantial fatigue (OR 2.2; 95% CI 1.9-2.6 and OR 3.6; 95% CI 3.2-4.2 respectively) according to their scores on the Chalder fatigue scale.[21, 230] Between 1.0-2.9% of Gulf War veterans reported symptoms consistent with chronic fatigue as a medical condition {prevalence difference all subjects 1.4 (0.9-2.0)}, and the differences between the Gulf War and comparison groups were more marked in the National Guard/Reserve than in the regular military.[16] All the criteria for chronic fatigue syndrome were met by 8 subjects in a study of 1155 Gulf War veterans and 2520 non-deployed personnel that investigated the prevalence of a chronic multisymptom illness, for which chronic fatigue was a key feature. Of these, 7 also were classified as severe cases and 1 as a mild-moderate case of this chronic multisymptom illness.[73] Whilst direct comparisons of our findings with those of previous studies are limited because of the different definitions used, chronic fatigue syndrome is self-reported less commonly by Australian than UK Gulf War veterans, but the risk of chronic or substantial fatigue is similar in Australian and overseas Gulf War veterans.

Thus, although fatigue as a symptom and as a medical condition has been reported to be more common among Gulf War veterans than non-Gulf veterans in previous studies, comprehensive and clinical evaluation of fatigue or chronic fatigue in these studies of Gulf War veterans has been limited. The risk of chronic fatigue syndrome in Gulf War veterans in our study (adjusted OR 5.0) is greater than the risk of chronic fatigue-related medical conditions that have been reported in any of these overseas studies.

The prevalence of chronic fatigue in primary care has been estimated to be 5.7%-27%.[391] The proportions of both study groups in our study reporting chronic fatigue (7.9% vs 4.2%) are at the lower end of the estimates.[391] The community prevalence of chronic fatigue

syndrome in US and UK populations has been estimated to be 0.2% to 0.7%[391] and this prevalence is slightly lower than that found in our Gulf War veteran study group (0.8%) but similar to that found in our comparison group (0.1%). These study populations are, however, different to those of our study; and a strength of our study is the use of a comparison group to whom the same definitions were applied in the same manner.

Although the cause of chronic fatigue syndrome remains unexplained, an association with a variety of immunological changes have been reported.[231] It has been hypothesised that chronic fatigue symptoms reported by veterans may be due to a shift in the T cell cytokine profile from a Th1 to a Th2 response.[228] As discussed in chapter 4, one stimulus that has been proposed as a potential instigator of this shift in cytokine production is administration of Th2-inducing vaccines, particularly those with a large antigen load (eg plague, anthrax, typhoid, tetanus and cholera) and/or those which used pertussis as an adjuvant. Another potential stimulus proposed is stress, as cortisol drives a Th2 response. Exposure to carbamate or organophosphate insecticides has also been suggested as a possible trigger, as these compounds inhibit IL-2 driven events required for Th1 function.[228]

A few studies have examined this in Gulf War veterans. One of these examined the peripheral blood T-cell cytokine production and the NK cell activity of Danish Gulf War veterans and found no difference between Gulf War veterans and controls.[168] However, the investigators did not specify whether or not the veterans included in the study had somatic or psychological symptoms. Another study[169] examined T cells, B cells, NK cells and cytokines in individuals with chronic fatigue syndrome (either Gulf War or non-Gulf War veterans) and in healthy Gulf War or non-Gulf War veteran controls. The authors concluded that there was no evidence of immune dysfunction in sporadic chronic fatigue syndrome, but that Gulf War veterans with severe fatiguing illness did have an altered immune function, although their results were still within the normal range.

Even though some of the other studies have done further tests, eg cytokine levels, the similarity of our results for CFS cases in the Gulf War veterans and the comparison group do not provide a strong rationale for further laboratory investigation of these cases at this stage.

14.5.1 Summary of findings

In summary, and in answer to the research questions, Australian Gulf War veterans have significantly more chronic fatigue syndrome than the comparison group according to the definition based on the Fakuda *et al* criteria used in our study, but the numbers were very small. Gulf War veterans also have significantly more prolonged fatigue, chronic fatigue, and medically unexplained chronic fatigue that did not fulfil the severity or associated symptoms criteria for chronic fatigue syndrome, ie more idiopathic chronic fatigue, than the comparison group.

The number of Gulf War veterans with chronic fatigue syndrome was too small to undertake further subanalysis in relation to exposures or experiences that occurred in the Gulf War.

The immunological profile of Gulf War veterans with chronic fatigue syndrome differed to that of comparison group subjects with chronic fatigue syndrome on one lymphocyte subset, (CD19, a B cell marker), but the clinical significance of this is uncertain.

The reasons for the increased risk of all fatigue-related conditions in Gulf War veterans are not obvious from the limited subgrouping according to lymphocyte subsets that could be done given the small numbers of cases of chronic fatigue syndrome. We would like to undertake further evaluation of cases of chronic fatigue and idiopathic fatigue, for whom

there are greater numbers of subjects, to investigate the characteristics and exposures of those at increased risk.

15. Health of female Gulf War veterans

This chapter describes the contact and recruitment outcomes, exposure assessment and investigation of health outcomes for female Gulf War veteran and comparison group participants. The results for female participants have been presented separately from male participants because health patterns in men and women can be quite different. If the data for the female participants had been included with the men's data, patterns specific to women would have been difficult to identify. Because the number of female Gulf War veterans is quite small, comparisons between the two groups are limited to primarily descriptive analyses. Tests to detect statistically significant differences between groups were not conducted because of these small numbers.

The study methods and definitions in relation to health outcomes for female participants in the study are generally the same as those described in the preceding chapters for the health of male Gulf War veterans and will not be repeated in this female health chapter. Where analyses and methods in relation to the investigation of women's health do differ from those described in previous chapters, these differences are documented in the appropriate section of this chapter.

15.1 Aim

The aim of this analysis is to describe the health of female Gulf War veterans and the exposures and experiences which they report as being relevant to their deployment to the Gulf War. Further, the analysis aims to compare the health, exposures and experiences of female Gulf War veterans with that of female comparison group participants. Finally, the analysis aims to compare the health, exposures and experiences of female Gulf War veterans with that of male Gulf War veterans.

15.2 Research questions

1. Are female Gulf War veterans similar to female comparison group participants in relation to a range of psychological and physical health measures?
2. What exposures and experiences do female Gulf War veterans report for the Gulf War deployment?
3. Are female Gulf War veterans similar to female comparison group participants in relation to exposures and experiences reported for non-Gulf War military service or civilian occupations?
4. Are female Gulf War veterans similar to male Gulf War veterans in relation to a range of psychological and physical health measures and exposures and experiences reported for the Gulf War deployment?

15.3 Results

15.3.1 Recruitment

The Australian deployment to the Gulf War included 38 female ADF personnel. These included 21 women who deployed with the Navy, 8 who deployed with the Army and 9 who deployed with the Air Force. During the contact and recruitment phase of the study, no

female Gulf War veterans were reported to be deceased, permanently overseas or found to be ineligible for participation in the study.

The originally selected comparison group for the study included 75 women. One of these was found to be ineligible for participation as she had not been a serving member of the ADF in August 1990; therefore the eligible sample of female comparison group subjects comprised 74 persons. A further one female comparison group subject was reported to be overseas long term, leaving 73 recruitable female comparison group subjects which included 28 Navy, 18 Army and 27 Air Force personnel. No female comparison group subjects were reported to be deceased.

The recruitment outcomes, for the female recruitable subjects for both study groups, are shown in Table 15.1. These recruitment outcomes are similar in pattern to those for males. In total, 32 (84.2%) female Gulf War veterans participated in the study, either through completion of both the postal questionnaire and medical assessment (78.9%) or through completion of the postal questionnaire alone (5.3%). The participation rate amongst female comparison group subjects was 54.8%, with 40 subjects participating. This included 32 (43.8%) female comparison group subjects who completed both the postal questionnaire and medical assessment, and a further eight (11%) female comparison group subjects who completed the postal questionnaire alone.

Table 15.1 Recruitment results for female Gulf War veterans and comparison group subjects.

Recruitment outcomes: females						
	Gulf War veterans		**Comparison group**		**Total females**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**
Total recruitable sample	**38**	**-**	**73**	**-**	**111**	**-**
Participants						
Full participant	30	(78.9)	32	(43.8)	**62**	**(55.9)**
Postal quest only	2	(5.3)	8	(11.0)	**10**	**(9.0)**
Non-participants						
Telephone quest only	1	(2.6)	10	(13.7)	**11**	**(9.9)**
Declined all participation	3	(7.9)	16	(21.9)	**19**	**(17.1)**
Non-responders	0	(0)	2	(2.7)	**2**	**(1.8)**
Non-contactables	1	(2.6)	5	(6.8)	**6**	**(5.4)**

15.3.2 Demographic, socioeconomic and lifestyle factors

Differences between the two groups in the patterns of demographic, socioeconomic and lifestyle factors were assessed for all 32 female Gulf War veterans and 40 female comparison group participants.

Female Gulf War veterans were slightly older than female comparison group participants with a mean age of 37.8 years compared with 35.8 years. The breakdown of female Gulf War veterans and comparison group participants into age categories at the time of participation in the study, and also service type and rank at the time of the Gulf War, are shown in Table 15.2.

Participating female Gulf War veterans were more likely to be from the Navy and less likely to be from the Air Force, than female comparison group participants. Participating female Gulf War veterans were also more likely to have a higher rank and less likely to have a lower rank, than participating female comparison group subjects.

Table 15.2 Age at the time of participation, and service type and rank at the time of the Gulf War, for female Gulf War veterans and comparison group participants.

Age, service type and rank				
	Gulf War veterans N=32		**Comparison group N=40**	
	n	**(%)**	**n**	**(%)**
Age at participation				
< 35	16	(50.0)	25	(62.5)
≥ 35	16	(50.0)	17	(42.5)
Service Type				
Navy	17	(53.1)	16	(40.0)
Army	8	(25.0)	8	(20.0)
Air Force	7	(21.9)	16	(40.0)
Rank				
Officer	13	(40.6)	12	(30.0)
Other rank-supervisory	10	(31.3)	9	(22.5)
Other rank-non supervisory	9	(28.1)	19	(47.5)

In relation to additional demographic measures (data not shown) approximately 85% of participants in both groups were born in Australia and four comparison group participants (10%), but no Gulf War veterans, identified themselves as being of aboriginal or Torres Strait Islander origin. Two thirds of the participants in both groups were married or in defacto relationships.

Gulf War veterans had achieved slightly higher levels of education than the comparison group, with 40% of Gulf War veterans reporting that they had attained an undergraduate or postgraduate degree compared with 30% of the comparison group. More than 80% of the female Gulf War veterans and 70% of the comparison group were currently in part-time of full-time employment. Only three subjects in total (one Gulf War veteran and two comparison group participants) reported that were not working due to ill-health.

Twenty five percent of female comparison group participants were current smokers and further 25% were former smokers. Gulf War veterans were less likely (18.8%) to be current smokers and more likely (34.4%) to be former smokers. Mean number of pack years for current smokers were 11.9 for Gulf War veterans and 20.4 for the comparison group. Mean number of pack years for former smokers were 13.4 for Gulf War veterans and 8.1 for the comparison group.

15.3.3 Reported Gulf War and other exposures

Gulf War and other exposures were self-reported in the postal questionnaire and assessed for all 32 female Gulf War veteran participants and 40 female comparison group participants.

15.3.3.1 Service characteristics of female Gulf War veterans during the Gulf War

Female Gulf War veteran participants included 17 Navy, 8 Army and 7 Air Force personnel. Of these, 20 females reported to have deployed to the Gulf War in ships; seven in the supply ship HMAS *Westralia* and thirteen in the hospital ship USNS *Comfort*.

Personnel attached to HMAS *Westralia* reported various job descriptions including radio operations and engineering.

All 13 females on USNS *Comfort* reported that their primary duties were medical related.

Five Army participants reported serving as part of Operation Habitat and all reported that their primary duties were medical related.

Six of the seven Air Force females served with 33 Squadron and most reported to be flight stewards on standby to evacuate Australian personnel if necessary.

Most female Gulf War veterans (91%) were still on deployment in the Gulf region at the time of the start of the air war on January 17th 1991.

15.3.3.2 Other active deployments

Four female Gulf War veterans (13%) and seven comparison group participants (18%) had been on one or more active deployments other than the Gulf War. These included deployments to East Timor, Korea, Malaysia, the Gulf area outside of the time of the Gulf War, Solomon Islands, Somalia, Thailand and Vietnam.

15.3.3.3 Immunisations and preventive medications reported for the Gulf War deployment

Female Gulf War veterans estimated receiving a median of seven immunisations for the Gulf War deployment (range 0 to 11), similar to the median of six estimated by the men. Four female Gulf War veterans (13%) reported receiving no immunisations at all, whereas twelve (38%) reported receiving a cluster of more than five immunisations within a period of one week or less, in a time period prior to deployment.

Gulf War veterans were provided with a list of types of immunisations from which respondents reported which ones they believed they had received as part of the Gulf War deployment. Participants also reported whether or not they had received anti-nerve agent pills (NAPS), anti-biological warfare tablets or anti-malarial medications. The results are shown in Table 15.3 and are very similar to those reported for male Gulf War veterans. The most common immunisations reported by female Gulf War veterans were those for cholera, typhoid, Hepatitis B and polio and these include three of the most common immunisations reported by male Gulf War veterans. For all listed immunisations, more than 20% of the female veterans did not know whether they had received them or not. This percentage was as high as 40% or more in relation to pertussis, MMR and anthrax and these immunisations were also commonly included in the "Don't know" category by male Gulf War veterans. Female veterans were a little less likely than the male veterans to report that they received anthrax and plague.

In relation to medications, no female participants reported taking anti-biological warfare tablets whereas six percent of the men reported taking these. Women were also less likely than the men to report taking NAPS and antimalarials.

Only two female Gulf War veterans reported having a 'significant' reaction to an immunisation or medication (data not shown).

Table 15.3 Immunisations and medications reported by female Gulf War veterans

Immunisations and medications (N=32)*						
	Yes		No		Don't know	
	n	(%)*	n	(%)*	n	(%)*
Immunisations						
Cholera	21	(67.7)	2	(6.3)	8	(25.8)
Typhoid	20	(64.5)	3	(9.7)	8	(25.8)
Hepatitis B	18	(60.0)	6	(20.0)	6	(20.0)
Polio (oral Sabin)	18	(60.0)	4	(13.3)	8	(26.7)
Diptheria, Tetanus (ADT)	17	(53.1)	6	(20.0)	7	(23.3)
Hepatitis A (Havrix)	12	(40.0)	9	(30.0)	9	(30.0)
Smallpox	12	(40.0)	9	(30.0)	9	(30.0)
Plague	8	(25.8)	14	(45.2)	9	(29.0)
Tuberculosis (BCG)	5	(17.2)	13	(44.8)	11	(37.9)
Measles, Mumps, Rubella (MMR)	5	(16.1)	13	(41.9)	13	(41.9)
Pertussis	3	(10.3)	12	(41.4)	14	(48.3)
Anthrax	3	(10.0)	15	(50.0)	12	(40.0)
Any other immunisation	19	(65.5)	1	(3.4)	9	(31.0)
Preventive medications						
Antimalarials	11	(34.4)	14	(43.8)	7	(21.9)
Anti-nerve agent pills (NAPS)	6	(18.8)	22	(68.8)	4	(22.5)
Anti-biological warfare tablets	0	(0)	27	(84.4)	5	(15.6)

* The value of N from which each percentage is derived may vary by up to 3 fewer respondents for individual table items.

15.3.3.4 Self reported psychological stressors during Gulf War service and during non Gulf War service

Military Service Experience questionnaire items reported by five or more female Gulf War veterans in relation to the Gulf War deployment, are shown in Table 15.4 in decreasing order of frequency. Total numbers of "yes" responses to individual items are quite small and therefore discussion of differences between Gulf War service versus non-Gulf War service, and between the two study groups in relation to non-Gulf War service, are limited to items where the differences are most apparent.

Items relating to fear or threat of attack including artillery or missile attack or biological or chemical attack, and fear for ones life including fear of entrapment below the waterline of a ship, were commonly reported in relation to the Gulf War deployment and rarely reported in relation to non-Gulf War military service. Feeling cut off or separated from family or significant others was the most common psychological stressor reported in relation to the Gulf War deployment. This item was common in relation to non-Gulf War service also, but only half as common compared with the Gulf War deployment.

Most items were more commonly reported in relation to the Gulf War deployment when compared to non-Gulf War service. The rarity of combat-type stressors or exposures during non-Gulf War service is probably related to the finding that very small numbers of female

Gulf War veterans had been on active deployment other than the Gulf War, and very small numbers of comparison group participants had ever been on an active deployment.

Sexual harassment was very common. It was more likely to be reported by females in the comparison group (50%), compared with Gulf War veterans during Gulf War service (23%) or during non-Gulf war service (24%), and more likely to be reported by female participants in both study groups when compared with male participants (<3%).

In other comparisons with male Gulf War veterans in relation to the Gulf War deployment, female Gulf War veterans were more likely to report feeling not sufficiently trained or prepared and less likely to report a 'near miss' or 'close call' incident, encountering undetonated mines or being responsible for detecting incoming attacks or spotting sea-mines. However, the four most common MSE items reported by female Gulf War veterans were also the four most common MSE items reported by male Gulf War veterans, though in a differing order.

Table 15.4 "Yes" responses to Military Service Experience questionnaire items.

Military Service Experience questionnaire						
	Gulf War service		Non-Gulf War service			
	Gulf War veterans N=32*		Gulf War veterans N=30*		Comp group N=40*	
MSE item	**n**	**(%)***	**n**	**(%)***	**n**	**(%)***
You felt cut off or separated from family or significant others.	20	(62.5)	9	(31.0)	15	(37.5)
You were in fear of artillery, missile, SCUD rocket or bomb attack.	18	(56.3)	0	(0)	0	(0)
You were on formal alert for, or felt in threat of nuclear, biological or chemical agent attack.	16	(50.0)	0	(0)	2	(5.0)
You were on a ship or aircraft (including a helicopter) passing through hostile waters or air space.	16	(50.0)	2	(6.9)	5	(12.5)
You felt not sufficiently trained or prepared for military activities.	15	(46.9)	5	(17.9)	11	(27.5)
You were in fear for your life.	14	(45.2)	3	(10.7)	1	(2.5)
On board a ship you feared death, injury or entrapment below the waterline as a result of missile attack or hitting a sea-mine.	14	(43.8)	0	(0)	0	(0)
You experienced lack of leadership in your team, crew or unit.	11	(34.4)	9	(30.0)	15	(37.5)
You felt lack of togetherness or cohesion in your team or unit.	10	(32.3)	12	(41.4)	14	(35.0)
You saw Defence personnel or civilians who were killed, dead, dying or maimed.	10	(31.3)	9	(31.0)	7	(17.5)
Your supplies or equipment were inadequate, insufficient or faulty.	9	(28.1)	4	(13.8)	9	(23.1)
You were sexually harassed.	7	(22.6)	7	(24.1)	20	(50.0)

Military Service Experience questionnaire						
	Gulf War service		Non-Gulf War service			
	Gulf War veterans N=32*		Gulf War veterans N=30*		Comp group N=40*	
MSE item	**n**	**(%)***	**n**	**(%)***	**n**	**(%)***
You were required to administer medical aid for which you were not adequately trained or equipped, eg geriatrics, paediatrics, palliative care.	7	(21.9)	2	(6.9)	1	(2.5)
You felt alienated from other military personnel around you.	7	(21.9)	7	(24.1)	6	(15.0)
Artillery, rockets, missiles, mines or something similar, exploded in the air, in the water or on the ground close to you.	6	(19.4)	0	(0)	2	(5.0)
You experienced a 'near miss' or 'very close call' incident where you were in imminent danger of being injured or killed.	6	(18.8)	5	(17.2)	4	(10.0)
You handled or came into contact with POWs or displaced refugees.	6	(18.8)	1	(3.4)	3	(7.5)
You had difficulty breathing as a result of exposure to oil, smoke, fumes, dust or other contaminants in the air.	6	(18.8)	2	(6.9)	3	(7.7)
You feared attack from bandits, rebels or other local militia groups.	6	(18.8)	3	(10.7)	4	(10.0)
You felt overwhelmed by the level of destruction or devastation or disease around you.	5	(16.7)	3	(10.7)	2	(5.0)
You encountered undetonated mines, including sea mines, or booby traps while on patrol or at your duty station.	5	(15.6)	0	(0)	0	(0)

* The value of each N from which each percentage is derived may vary by up to 2 fewer respondents for individual MSE questionnaire items.

15.3.3.5 Self reported chemical and environmental exposures during the Gulf War and other active deployments

Chemical and environmental exposures reported by four or more female Gulf War veterans in relation to the Gulf War deployment, are shown in Table 15.5 in decreasing order of frequency. Because only four female Gulf War veterans and seven comparison group participants had been on one or more active deployment other than the Gulf War, chemical and environmental exposures reported in relation to those deployments were too few to be compared and they have not been tabulated.

Female Gulf War veterans reported a range of exposure types including locally supplied foods, insects, sunscreens, SMOIL, fuels, solvents and pesticides. Compared with male Gulf War veterans, female Gulf War veterans were more likely to report exposure to SMOIL and pesticides and less likely to report exposure to solvents, fuels, engine exhausts and dust storms.

Possible exposure to depleted uranium was very rare and no female Gulf War veterans reported exposure to CARC paint or wearing flea collars.

Table 15.5 Chemical and environmental exposures reported by female Gulf War veterans in relation to the Gulf War deployment

Gulf War deployment chemical and environmental exposures		
	Gulf War veterans N=32	
	n	**(%)**
Ate locally sourced, non-military issue food eg from local villagers.	24	(75.0)
Bitten by flies, sand flies, fleas, mosquitoes or other insects	18	(56.3)
Used a sunscreen when outdoors	17	(53.1)
Exposed to SMOIL	17	(53.1)
Exposed to intense smoke eg from forest fires or burning oil	12	(37.5)
Undertook refuelling	12	(37.5)
Ate locally sourced, military issue food	10	(31.3)
Swam or bathed in local lakes, rivers or the sea	9	(28.1)
Drank water from local taps or wells	8	(25.0)
Had solvents, oils, diesel or other fuel on your skin	7	(22.6)
Exposed to solvents eg from cleaning or painting	7	(21.9)*
Clothing or uniforms treated with pesticides	5	(15.6)
Lived or worked in an area that had been recently sprayed or fogged with a pesticide	5	(15.6)
Tent treated with pesticides	4	(12.5)
In an area where chemical warfare agents had probably been used	4	(12.5)

* For this item N=31

15.3.3.6 Other occupational exposures during military postings and during civilian occupations

Self reported exposure to pesticides, solvents, fuels and exhausts during military postings of three months or more are shown in Table 15.6. Exposure to solvents and exhausts were relatively common in both study groups, reported by between 20% and 31% of all participants. Exposure to pesticides was relatively common in the Gulf War veteran group but less common in the comparison group.

In relation to civilian occupations (data not shown), exposure to chemical agents such as pesticides, solvents and fuels were rare in both study groups. Exposure to infectious diseases and to trauma to others were both reported by more than 40% of female Gulf War veterans and by only 12% of the comparison group.

Table 15.6 Self reported exposures during military postings of 3 months or more.

Military postings exposures				
	Gulf War veterans N=32		Comparison group N=40	
	n	(%)	n	(%)
Pesticides	6	(18.8)	2	(5.0)
Solvents	10	(31.3)	11	(27.5)
Fuels	7	(21.9)	6	(15.0)
Engine exhausts	9	(28.1)	8	(20.0)

15.3.4 General health

The 32 female Gulf War veterans and 40 female comparison group participants were assessed for differences in their self report of health symptoms experienced in the previous month, doctor diagnosed or treated medical conditions that were first experienced in 1991 or later, number of hospitalisations in the previous twelve months, functional impairment due to illness in the previous two weeks, current use of medication and Short-Form-12 Health Survey summary scores.

The 30 female Gulf War veterans and 32 female comparison group participants, who attended HSA for the medical assessment, were assessed for differences in measures of height, weight and Body Mass Index, waist and hip circumference and hip-to-waist ratio, blood pressure and fitness test results.

15.3.4.1 Symptoms

Table 15.7 presents those health symptoms reported to be experienced in the previous month by at least five female Gulf War veterans or more, and ordered by decreasing prevalence for the Gulf War veteran group. This includes 32 of the 63 health symptoms included in the postal questionnaire. The prevalences of these 32 symptoms are also shown for the comparison group. Gulf War veterans reported 17 of the 32 symptoms more commonly than the comparison group, whilst the comparison group reported 14 symptoms more commonly.

Table 15.7 Self-reported symptoms in the previous month

Self-reported symptoms				
	Gulf War veterans N=32		Comparison group N=40	
Symptom	**n**	**(%)**	**n**	**(%)**
Fatigue	21	(65.6)	27	(67.5)
Headaches	19	(59.4)	28	(70.0)
Irritability / outbursts of anger	18	(56.3)	19	(47.5)
Sleeping difficulties	18	(56.3)	23	(57.3)
Low back pain	18	(56.3)	20	(50.0)
Feeling unrefreshed after sleep	16	(50.0)	21	(52.5)
Loss of interest in sex	14	(43.8)	11	(27.5)
Flatulence or burping	13	(40.6)	13	(32.5)
Indigestion	13	(40.6)	5	(12.5)
Forgetfulness	12	(37.5)	15	(37.5)
General muscle aches or pains	12	(37.5)	17	(42.5)
Difficulty finding the right word	11	(34.4)	15	(37.5)
Stiffness in several joints	11	(34.4)	14	(35.0)
Feeling jumpy / easily startled	10	(31.3)	8	(20.0)
Rash or skin irritation	9	(28.1)	9	(22.5)
Sore throat	9	(28.1)	12	(30.0)
Loss of concentration	9	(28.1)	13	(32.5)
Avoiding doing things or situations	9	(28.1)	5	(12.5)
Pain, without swelling or redness, in several joints	9	(28.1)	12	(30.0)
Stomach cramps	8	(25.0)	11	(27.5)
Intolerance to alcohol	7	(21.9)	6	(15.0)
Diarrhoea	7	(21.9)	7	(17.5)
Dizziness, fainting or blackouts	7	(21.9)	5	(12.5)
Feeling distant or cut off from others	6	(18.8)	6	(15.0)
Constipation	6	(18.8)	7	(17.5)
Mouth ulcers	6	(18.8)	1	(2.5)
Increased sensitivity to noise	6	(18.8)	3	(7.5)
Distressing dreams	6	(18.8)	8	(20.0)
Unintended weight gain greater than 4kg	6	(18.8)	4	(10.0)
Shortness of breath	5	(15.6)	9	(22.5)
Skin infections eg boils	5	(15.6)	0	(0)
Persistent cough	5	(15.6)	8	(20.0)

The six most prevalent symptoms for female Gulf War veterans were the same as the six most prevalent symptoms for male Gulf War veterans, and tended to be neuropsychological or musculoskeletal in nature. Whilst these were in different orders of prevalence, these six most prevalent symptoms affected between 50% and 66% of both male and female Gulf War veterans. Women were five times less likely than men to report ringing in the ears, three times less likely to report itchy or painful eyes, and twice as likely to report loss of interest in sex.

Only five symptoms, of the original 63, were not reported by any female Gulf War veterans as having been experienced in the previous month. These were double vision, shaking, seizures or convulsions, pain on passing urine and vomiting (not tabulated).

The median number of symptoms reported was 11.0 (range 0 – 27) for female Gulf War veterans and 10.5 (range 0 – 35) for female comparison group participants.

15.3.4.2 Medical conditions

Table 15.8 presents those medical conditions which were reported by three or more female Gulf War veterans as being doctor diagnosed or treated and first experienced in 1991 or later. These are ordered in decreasing prevalence for Gulf War veterans. This includes 15 of the 61 medical conditions in the postal questionnaire.

Total numbers of female subjects reporting medical conditions first experienced in 1991 or later were very small and therefore differences between the two groups are difficult to interpret. However, the largest differences between the two groups are in relation to reported psychological conditions, with female Gulf War veterans reporting more posttraumatic stress disorder, anxiety, stress and depression and other psychiatric or psychological conditions needing treatment or counselling. Gulf War veterans were also more likely to report yeast disease or candidiasis.

Table 15.8 Self-reported doctor diagnosed or treated medical conditions first experienced in 1991 or later

Medical conditions diagnosed in 1991 or later				
	Gulf War veterans N=32*		Comparison group N=40*	
Medical condition	**n**	**(%)***	**n**	**(%)***
Back or neck problems	9	(33.3)	13	(41.9)
Period problems	9	(33.3)	9	(27.3)
Anxiety, stress or depression	10	(31.3)	8	(20.0)
Miscarriages	5	(17.9)	6	(15.4)
Joint problems	5	(17.2)	6	(17.1)
Bronchitis	4	(13.3)	3	(8.8)
Dermatitis	4	(13.3)	5	(13.5)
Irritable bowel syndrome	4	(12.9)	4	(10.0)
Any other skin problem†	4	(12.9)	5	(13.5)
Other psychiatric or psychological condition needing treatment or counselling‡	4	(12.9)	1	(2.5)
Hayfever	4	(12.9)	3	(10.3)
Yeast disease or candidiasis	4	(12.5)	1	(2.9)
Migraines	3	(10.3)	3	(8.1)
Post Traumatic Stress Disorder	3	(9.4)	1	(2.5)
Any disease of the genital organs	3	(9.4)	5	(12.5)

* The value of each N from which each percentage is derived may vary by up to 9 fewer respondents for individual medical conditions.
† Refers to skin conditions other than dermatitis, eczema, psoriasis, malignant melanoma or other skin cancer as reported by the participant in the postal questionnaire.
‡ Refers to psychiatric or psychological conditions other than alcohol abuse or dependency, drug abuse or dependency, anxiety stress or depression, or posttraumatic stress disorder as reported by the participant in the postal questionnaire

In comparison with male Gulf War veterans, and excluding those medical conditions asked specifically of women, the most prevalent conditions reported by women were similar to the most prevalent conditions reported by men. 'Back or neck problems' was the most prevalent condition reported by male Gulf War veterans, 'anxiety stress or depression' was the 4th most prevalent condition reported by men and 'joint problems' was the 2nd most prevalent. Other highly prevalent conditions reported by female Gulf War veterans as being first diagnosed in 1991 or later; namely dermatitis, hayfever, other psychological disorders, posttraumatic stress disorder and migraines, were all amongst the 16 most prevalent conditions reported by male Gulf War veterans.

Of these medical conditions specific to women, miscarriage and period problems were similar in the two groups.

15.3.4.3 Hospitalisations, functional impairment and use of medications

In the twelve months prior to assessment, eight (25%) female Gulf War veterans and nine (22.5%) comparison group participants reported being hospitalised overnight or longer. Amongst Gulf War veterans, one subject was hospitalised for 170 days across the 12 months; the other seven Gulf War veterans averaged 5 days. The comparison group averaged 3 days of hospitalisation.

In the two weeks prior to assessment, eleven (34.4%) female Gulf War veterans and twelve (30%) comparison group participants reported staying in bed or at home all or part of any day because they did not feel well or as a result of illnesses or injury.

Twenty (62.5%) female Gulf War veterans and sixteen (40%) comparison group participants reported that they were currently taking medicines including tablets, creams, inhalers or other drugs.

Whilst there is no apparent difference between the two groups regarding average hospitalisations in the previous 12 months and functional impairment in the previous two weeks, slightly more female Gulf War veterans report greater use of medications than female comparison group participants.

15.3.4.4 Short-Form-12 Health Survey (SF-12)

Using the SF-12, female Gulf War veterans reported similar physical health but poorer mental health than the comparison group. Mean scores for the Physical Component Summary of the SF-12 were 50.6 (SD 10.2) for Gulf War veterans and 49.4 (SD 8.1) for the comparison group. Mean scores for the Mental Component Summary of the SF-12 were 46.1 (SD 10.1) for Gulf War veterans and 51.3 (SD 10.2) for the comparison group. The mean SF-12 scores for women and pattern of poorer MCS scores found for Gulf War veterans, are similar to the mean scores and pattern found for the men.

15.3.4.5 Height, weight and Body Mass Index

The two female study groups were very similar in relation to mean height, weight and Body Mass Index (BMI). Gulf War veterans were, on average, slightly taller (166cm versus 164cm) and slightly heavier (73.7kg versus 70.5kg) than the comparison group, however both groups recorded the same mean BMI of 26.

Table 15.9 Weight category using BMI ranges

Weight category using BMI				
	Gulf War veterans		Comparison group	
BMI (kg/m^2)	**n**	**(%)**	**n**	**(%)**
Normal weight				
18.5-<20.00	1	(3.3)	1	(3.1)
20.00-<25.00	9	(30.0)	10	(31.3)
Overweight or obese				
Pre-obese (25.00-<30.00)	14	(46.7)	18	(56.3)
Obese (>30.00)	6	(20.0)	3	(9.4)

Using the individual BMI results, participants were classified as either underweight, or into categories of ‘normal weight’ or ‘overweight or obese’ according to the criteria used by the

National Nutrition Survey.[289] No participants met criteria for being underweight (BMI ≤ 18.5). The results of the classification of participants into normal weight categories and overweight or obese categories are shown in Table 15.9. Approximately one third of both groups met criteria for normal weight. Of those remaining subjects classified as overweight, Gulf War veterans were slightly more likely than comparison group participants to meet criteria for obesity.

15.3.4.6 Waist, hip, and waist-to-hip ratio

Waist and hip circumferences were very similar for the two groups, averaging 86.3cm and 105.7cm for Gulf War veterans, and 83.4cm and 104.4cm for the comparison group. Gulf War veterans (n=8, 27%) were slightly less likely than the comparison group (n=13, 41%) to have a waist-to-hip ratio greater than 0.8 which is indicative of increased risk of cardiovascular disease.

15.3.4.7 Blood Pressure

More than 90% of females in both groups recorded normal blood pressure. Of those, more than 70% recorded optimal blood pressure readings of systolic pressure <120mmHg and diastolic pressure <80mmHg. Only two subjects in each group had high-normal blood pressure and only one subject from each group had mild, grade 1 hypertension. No female subjects had grade 2 or 3 hypertension or isolated systolic hypertension.

15.3.4.8 Fitness test

20 female Gulf War veterans (66.7%) and 23 female comparison group participants (53.1%) completed a three-minute step test. The mean recovery heart rate was similar for the two groups at 146.9 bpm and 148.5 bpm respectively.

The two groups are shown in Table 15.10 after dividing the range of recovery heart rates into tertiles, with lower recovery heart rates representing higher fitness. The two groups had a very similar pattern of fitness.

Table 15.10 Step test recovery heart rates

Step test recovery heart rate				
	Gulf War veterans N=20		Comparison group N=17	
Mean recovery heart rate	n	(%)	n	(%)
112 ≥139 (Higher fitness)	7	(35.0)	5	(29.4)
140 ≥158 (Medium fitness)	7	(35.0)	6	(35.3)
159 ≥180 (Lower fitness)	6	(30.0)	6	(35.3)

15.3.5 Laboratory investigations

Laboratory investigations were performed on blood samples drawn from the 30 female Gulf War veterans and 32 female comparison group participants who undertook the medical assessment. No female participants declined to give blood samples.

Mean scores for all haematological, biochemistry and liver function tests are shown in Table 15.11 and are very similar between the two groups of female participants.

All parameters were reviewed for the numbers of subjects falling inside and outside of the reference ranges for each test (data not shown). The pattern of results were very similar for the two groups and very similar to those presented for the male study participants. The numbers of subjects outside of the reference ranges were typically very small and too few for any differences between the two groups to be meaningfully assessed.

Table 15.11 Haematological, biochemistry and liver function test results

		Gulf War veterans (N=30)		Comparison group (N=32)	
Parameter	Reference range	**Mean**	**(SD)**	**Mean**	**(SD)**
Haematological tests					
Haemoglobin (Hb)	115-155 g/L	131.8	(9.8)	134.3	(10.8)
Mean corpuscular volume (MCV)	80.0-98.0 fl	92.8	(8.1)	93.4	(2.9)
Mean corpuscular haemoglobin (MCH)	27.0-33.0 pg	29.8	(2.7)	30.3	(1.3)
White cell count (WCC)	4.0-11.0 x 10^9/L	6.7	(1.5)	6.7	(1.7)
Neutrophil count	1.8-7.5 x 10^9/L	4.2	(1.2)	4.0	(1.3)
Lymphocyte count	1.0-3.5 x 10^9/L	2.0	(0.5)	2.1	(0.7)
Eosinophils	0.02-0.5 x 10^9/L	0.1	(0.1)	0.2	(0.1)
Basophils	0.0-0.1 x 10^9/L	0.03	(0.01)	0.02	(0.01)
Monocytes	0.2-0.8 x 10^9/L	0.4	(0.1)	0.4	(0.1)
Platelets	150-400 x 10^9/L	263.6	(61.9)	269.6	(61.5)
Erythrocyte sedimentation rate (ESR)	1-12mm/hour†	5.7	(3.3)	6.6	(7.2)
Biochemical tests					
Sodium	137-145 mmol/L	140.9	(2.2)	140.3	(2.4)
Potassium	3.8-4.9 mmol/L	4.2	(0.4)	4.4	(0.5)
Urea	2.7-8.0 mmol/L	4.4	(0.9)	4.8	(1.0)
Creatinine	0.05-0.12 mmol/L	0.1	(0.01)	0.1	(0.01)
Ionised calcium	1.10-1.25 mmol/L	1.1	(0.1)	1.1	(0.1)
Phosphate	0.65-1.45 mmol/L	1.1	(0.2)	1.2	(0.2)
Random plasma glucose	5.5-11.0 mmol/L*	5.0	(1.3)	4.5	(0.6)
C-reactive protein	<4-10 mg/L	3.4	(3.0)	3.1	(2.5)
Liver function tests					
Albumin	34-48 g/L	39.8	(2.1)	40.4	(3.3)
Globulin	26-41 g/L	30.2	(3.5)	30.3	(3.8)
Total protein	65-85 g/L	70.1	(3.5)	70.7	(5.5)
Total bilirubin	6-24 μmol/L	8.2	(3.4)	9.3	(4.2)
GGT	0-60 U/L	19.9	(13.4)	19.1	(12.9)
ALP	30-110 U/L	67.9	(25.3)	66.8	(21.1)
ALT	0-55 U/L	22.6	(10.3)	20.4	(11.2)
AST	0-45 U/L	26.0	(7.6)	25.3	(5.1)

* Reference ranges used are those recommended by the NHMRC (http://www.health.gov.au/nhmrc/ advice/pdf/type2.pdf).
† ESR reference intervals are 1-12mm/hour (age ≤50 years) and 1-20mm/hour (age >50 years)

15.3.6 Psychological health

15.3.6.1 CIDI-defined psychological disorders

All 30 female Gulf War veterans and 32 female comparison group participants, who attended HSA for the medical assessment component of the study, completed the psychologist administered CIDI interview. The numbers and percentages of female Gulf War veterans and comparison group participants who met criteria for CIDI-defined pre-Gulf War disorders, post-Gulf War disorders and disorders present within the previous 12 months, are shown in Table 15.12. Where no female subjects met criteria for a particular type of disorder, this disorder was excluded from the table.

Table 15.12 Female Gulf War veterans and comparison group participants with CIDI-defined pre-Gulf War disorders, post-Gulf War disorders and disorders present within the previous 12 months.

CIDI defined psychological disorders												
	Pre-Gulf War disorders				Post-Gulf War disorders				Disorders present in previous 12 months			
CIDI defined disorder	Gulf War veterans		Comp grp		Gulf War veterans		Comp grp		Gulf War veterans		Comp grp	
	n	(%)	n	(%)	n	(%)*	n	(%)*	n	(%)	n	(%)
Major depression	3	(10.0)	1	(3.1)	6	(22.2)	8	(25.8)	2	(6.7)	2	(6.3)
Posttraumatic stress disorder	0	(0)	1	(3.1)	3	(10.0)	2	(6.5)	2	(6.7)	0	(0)
Obsessive-Compulsive Disorder	0	(0)	0	(0)	2	(6.7)	0	(0)	2	(6.7)	0	(0)
Specific phobia	4	(13.3)	1	(3.1)	0	0	1	(3.2)	4	(13.3)	2	(6.3)
Social phobia	1	(3.3)	0	(0)	1	(3.4)	0	0	1	(3.3)	0	(0)
Panic disorder / Agoraphobia	1	(3.3)	0	(0)	1	(3.4)	1	(3.1)	1	(3.3)	1	(3.1)
Somatisation disorder	0	(0)	0	(0)	1	(3.3)	0	(0)	1	(3.3)	0	(0)
Alcohol dependence/ abuse	3	(10.0)	1	(3.1)	1	(3.7)	1	(3.2)	2	(6.7)	0	(0)
Hypochondriasis	0	(0)	0	(0)	0	(0)	1	(3.1)	0	(0)	1	(3.1)
Any CIDI disorder	10	(33.3)	4	(12.5)	5	(25.0)	9	(32.1)	9	(30.0)	4	(12.5)

* Percentage of those subjects who did not have a pre-Gulf War disorder of the same type.

The total numbers of female participants diagnosed with CIDI defined disorders were very small and too few for meaningful comparisons to be made between the two groups in regard to individual diagnoses. Female Gulf War veterans were more likely than comparison group participants to have had a CIDI defined pre-Gulf War disorder and were more likely to have had a disorder present within the previous twelve months. Amongst those participants who had not had any pre-Gulf War disorder, female Gulf War veterans and comparison group participants had a similar occurrence of post-Gulf War disorders.

Only three female Gulf War veterans (9.4%) and three female comparison group participants (10.0%) had more than one CIDI-defined post-Gulf War disorder (not tabulated).

15.3.6.2 GHQ-12, PCL-S and AUDIT

Female Gulf War veterans (n=15, 46.9%) were more likely than female comparison group participants (n=13, 32.5%) to meet GHQ-12 caseness criteria, predictive of a possible current psychiatric condition. Similar to the male participants in both groups, levels of current psychological morbidity, as measured by the GHQ, were greater than those measured by the CIDI. Female Gulf War veterans were slightly more likely than male Gulf War veterans to meet GHQ-12 caseness criteria.

Very few female Gulf War veterans (n=2, 6.9%) and female comparison group participants (n=1, 2.8%) met criteria for PCL-S caseness criteria, predictive of a possible current posttraumatic stress disorder.

Five (15.6%) female Gulf War veterans and six (15%) female comparison group participants met criteria for AUDIT caseness criteria, predictive of problem drinking. These prevalences are approximately one half of those reported for male study participants. Similar to the male participants in both groups, levels of current problem drinking, as measured by the AUDIT, were greater than those measured by the CIDI.

15.3.7 Respiratory health

15.3.7.1 Self reported respiratory symptoms and conditions

All 30 female Gulf War veterans and 32 female comparison group participants, who attended HSA for the medical assessment component of the study, completed the Respiratory Health Questionnaire which was administered by the attending HSA nurse. The results are shown in Table 15.13 and relate to self-reported respiratory symptoms experienced within the previous 12 months and respiratory medical conditions reported to be doctor diagnosed.

Total numbers of participants reporting respiratory symptoms or conditions were very small. The pattern of reporting of symptoms was very similar between the two groups. Female Gulf War veterans and comparison group participants were equally likely to report wheeze in the previous 12 months, however Gulf War veterans were more likely to report doctor diagnosed asthma. Nocturnal cough was the most common respiratory symptom, reported by approximately one third of participants in each study group.

Table 15.13 Respiratory symptoms and conditions

	Gulf War veterans N=32		Comparison group N=30	
	n	(%)	n	(%)
Symptoms				
Wheeze at any time	5	(15.6)	5	(16.7)
Nocturnal chest tightness	5	(15.6)	2	(6.7)
Nocturnal cough	9	(28.1)	10	(33.3)
Morning cough	4	(12.5)	3	(10.0)
Morning sputum	4	(12.5)	5	(16.7)
Spontaneous dyspnoea	3	(9.4)	2	(6.7)
Post-exertional dyspnoea	5	(15.6)	7	(24.1)
Conditions				
Doctor diagnosed asthma	7	(21.9)	3	(10.0)
Doctor diagnosed bronchitis	3	(9.4)	3	(10.0)

15.3.7.2 Spirometry

27 female Gulf War veterans and 29 female comparison group participants completed spirometry testing which met American Thoracic Society criteria. Mean FVC and FEV_1 values for the two groups were very similar. Mean (SD) FVC was 3.80L (0.56L) for Gulf War veterans and 3.70L (0.57L) for the comparison group. Mean (SD) FEV_1 was 3.01L (0.46L) for Gulf War veterans and 2.98L (0.44L) for the comparison group. These values in each group were similar to, or higher than those predicted for the females based on their age, height and race. No participants were assessed to have an obstructive disorder and two comparison group participants, but no Gulf War veterans, were assessed to have a restrictive disorder.

15.3.8 Neurological health

Neuropathic symptoms experienced within the previous four weeks, and self-reported by at least three female Gulf War veterans, are shown in Table 15.14. Very few female subjects reported neuropathic symptoms and therefore any comparisons between the two groups must be interpreted with caution. However, Gulf War veterans seemed to be less likely to report difficulty getting up from sitting, numbness and prickling sensations in the hands or arms and also numbness and prickling sensations in the in the feet and legs (data not shown) and more likely to report feeling unsteady walking in the dark.

The symptoms most commonly reported by females were similar to those most commonly reported by males.

No female participants from either group reported difficulty with undoing buttons, recognising hot from cold water or feeling pain, cuts or injuries.

The neuropathy impairment score was calculated for 29 female Gulf War veterans and 31 comparison group participants. Mean scores were similar at 2.0 (SD 4.4) and 2.7 (SD 7.0) respectively.

Table 15.14 Neuropathic symptoms experienced within the previous four weeks, and reported by at least three female Gulf War veterans.

Self-reported neuropathic symptoms				
	Gulf War veterans N=32		Comparison group N=40*	
Neuropathic symptom	**n**	**(%)**	**n**	**(%)***
Difficulty lifting objects high above your head or from a high shelf	5	(15.6)	5	(12.5)
Difficulty getting up from sitting in a chair or couch without the use of your arms	5	(15.6)	9	(23.1)
Feeling unsteady walking in the dark	5	(15.6)	3	(7.7)
Difficulty turning doorknobs or unscrewing jars	4	(12.5)	1	(2.5)
Numbness, "asleep feeling" or prickling sensation in your hands or arms	4	(12.5)	8	(21.1)
Burning, deep aching or tenderness in your feet or legs	3	(9.4)	5	(12.8)
Feeling like you will faint, or fainting, when you stand up from a lying or sitting position	3	(9.4)	4	(10.3)

* The value of N from which each percentage is derived may vary by up to 2 fewer respondents for individual symptoms.

15.3.9 Chronic fatigue and immunological investigations

One female Gulf War veterans was assessed as having 'chronic fatigue'; that is, extreme tiredness or fatigue that had been persistent, relapsing or recurring for at least 6 months or more since it first began.

15.3.10 Reproductive outcomes

Ten percent of females in each study group (three Gulf War veterans and four comparison group participants) reported fertility difficulties in the time period commencing 1991 or later. These rates were similar to those reported by male participants.

Five women in each group reported one or more miscarriage in the time period commencing 1991 or later. A small number of women in each group reported terminating a pregnancy.

Thirteen female Gulf War veterans (41%) and 22 female comparison group participants (55%) reported a total of 23 and 38 live births respectively for the time period commencing 1992 or later. Amongst the live births there were no subsequent deaths reported, no cancers, two (9%) premature births in children of Gulf War veterans, five (13%) premature births in children of comparison group participants, three (14%) and five (14%) cases of low birth weight in children of Gulf War veterans and comparison group participants respectively and two (9%) reported birth defects in children of Gulf War veterans.

15.3.11 Cohort study of mortality and cancer

The cohort of eligible study participants included 38 female Gulf War veterans and 73 female comparison group subjects. All were included in the matching process with data held by the National Death Index (NDI) and the National Cancer Statistics Clearing House (NCSCH). The time period for the cancer incidence and mortality matching was 1 January 1991 to 31 December 1998 for the NCSCH and to 31 December 2000 for the NDI.

One female comparison group subject was found to have a cancer diagnosis.

No female subjects in either study group were found to be deceased, according to the NDI match.

15.4 Discussion

Female Gulf War veterans comprised two percent of the entire Australian Gulf War deployment. Their roles were predominantly medical related, with many of the female Gulf War veterans serving in the Task Group Medical Support Element deployed to the US hospital ship USNS *Comfort* or with the ADF Operation Habitat in the provision of humanitarian aid to Kurdish refugees. Other roles included information technology support, radio operations, engineering and flight support in the Navy and Air Force.

The pattern of participation by females in this study was similar to that observed in the male sample, with participation rates of over 80% in the female Gulf War veterans' group and 55% in the female comparison group. The total number of female participants, however, was quite small with only 32 Gulf War veterans and 40 comparison group subjects participating. When total numbers are this small, prevalence rates can be affected substantially by the inclusion or exclusion of only a couple of subjects. Therefore it is very difficult to draw meaningful conclusions from any differences observed between the two female study groups.

The two study groups were, nonetheless, very similar in their demographic profiles, exposures assessment and health measures. There were also some marked parallels in the health and exposure patterns of female Gulf War veterans with those of male Gulf War veterans.

Female Gulf War veterans and comparison group participants had similar patterns of country of birth, marital status and employment status. However, participating female Gulf War veterans were, on average, a little older than the female comparison group participants, more likely to have held a senior rank at the time of the Gulf War and more likely to have attained a postgraduate degree.

Psychological stressors most commonly reported by women in relation to the Gulf War were similar to those reported by men, with the most prevalent items including fear for one's life and threat of attack including chemical or biological attack. Similar stressors were very rarely reported by female participants in both groups in relation to non-Gulf War service. This is probably related to the finding that only seven female comparison group participants had ever been on an active deployment, and only four female Gulf War veterans had been on an active deployment other than the Gulf War. Compared with men, female Gulf War veterans were more likely to report such stressors as feeling insufficiently prepared and incidents of sexual harassment in relation to the Gulf War deployment. During non-Gulf War military service, female Gulf War veterans were less likely than the comparison group to report experiences of sexual harassment.

The most common chemical and environmental exposures reported by women for the Gulf War deployment, included locally sourced, non-military issue food, insect bites, sunscreens and SMOIL. Female Gulf War veterans were more likely than the men to report exposure to SMOIL and this difference is likely to reflect the finding that more than 90% of female veterans were still in the Gulf region after the commencement of the air war in January 1991. Many, therefore, would still have been in the Gulf region when the Iraqis started setting fire to Kuwaiti oil wells in January and February. The hospital ship USNS *Comfort*, in particular, was reported to have been heavily clouded by SMOIL. Few female Gulf War veterans, however, reported related stressors or exposures such as difficulty breathing or burns or rashes on the skin as a result of smoke or oil in the air.

Compared with the men during the Gulf War, female Gulf War veterans reported higher pesticide exposure and lower solvent, fuel, engine exhausts and dust storm exposure. These differences may reflect different patterns of primary duties across the small female veteran group, compared with the much larger male veteran group.

In relation to immunisations received for the Gulf War deployment, female Gulf War veterans estimated receiving a median of six immunisations and these were most likely to include cholera, typhoid, Hepatitis B and polio. These patterns were similar to those reported by the men. Also similar to the men, many women did not know whether they had received some of the individual immunisations or not. The women were less likely, than the men, to report receiving immunisations for anthrax and plague, and NAPS and anti-malarial medications. No women, compared with six percent of the men, reported taking anti-biological warfare tablets during the Gulf War.

Female Gulf War veterans and comparison group participants reported similar exposures in relation to non-Gulf War military postings and civilian occupations, with the exception of a higher likelihood of exposure to infectious diseases and trauma reported by Gulf War veterans. This difference between the two female study groups is likely to be related to the higher proportion of health professionals in the Gulf War veterans' group.

The two female study groups reported very similar rates of recent general health symptoms and the most common symptoms were often also the most common symptoms reported by male participants. There were some differences in rates of neuropathic symptoms between female Gulf War veterans and comparison group participants, however total numbers were extremely small. Reporting of medical conditions was also similar between the two female study groups however Gulf War veterans reported slightly more psychological conditions than the comparison group and more doctor diagnosed asthma.

When psychological conditions were assessed further using the CIDI, female Gulf War veterans were slightly less likely, than the comparison group, to have a post-Gulf War psychological disorder but more likely to have a psychological disorder present in the previous 12 months. Female Gulf War veterans also scored more poorly on the SF-12 and GHQ-12 measures of recent mental functioning. Whilst small numbers of female participants make interpretation of these finding difficult, the findings are consistent with increased psychological morbidity in male Gulf War veterans and may, therefore, reflect an important difference between the two female study groups. Possible causes for poorer psychological health in female Gulf War veterans may include stress related to the Gulf War deployment, however the numbers of females with psychological conditions are too few for any investigations of Gulf War exposures to provide useful results.

Additional measures of health revealed few consistent or meaningful differences between the two female study groups. Female Gulf War veterans were more likely to report current use of medications. They were also assessed as less likely to have a waist-to-hip ratio indicative of increased risk of cardiovascular disease. Further measures of health, however, revealed no notable differences between the two groups; these included laboratory investigations of blood parameters, blood pressure, spirometry, step tests, height, weight and BMI, hip and waist circumference, assessment for chronic fatigue, reproductive outcomes, self reported hospitalisations, and cancer and mortality matches with the NCSCH and NDI.

As only 38 females in total served in the Australian deployment to the Gulf War, and as most participated in the study, there is little further research which can be done to improve the power of this study to detect true differences in health risks, or their possible causes, in female Gulf War veterans. However, it is important that female Gulf War veterans not be excluded from the broader findings and recommendations presented for male Gulf War veterans in this report. Whilst there are some differences in the exposures and health patterns reported between female and male Gulf War veterans, there are also some important similarities; particularly in relation to the pattern of symptom reporting, exposures to stressors during the Gulf War and increased psychological morbidity. The male and female Gulf War veteran groups, therefore, should be considered together as representing the complete experience of the Australian Defence Forces in the Gulf War.

15.4.1 Summary of findings

In summary, and in relation to the research questions for this chapter:

Amongst female Gulf War veterans there was some increased risk of recent psychological morbidity, higher reporting of some neuropathic symptoms and greater use of medication. Female Gulf War veterans were very similar to female comparison group participants on a range of other health measures including reported symptoms and objective investigations of blood parameters and lung function. Numbers of female participants, however, are too small for firm conclusions to be drawn about differences between the two groups.

In relation to the Gulf War deployment, female Gulf War veterans were most likely to report exposure to several immunisations, SMOIL, locally sourced foods and insects, and feelings of isolation, fear for their life and threat of biological or chemical attack.

Female Gulf War veterans reported greater civilian occupational exposure to infectious diseases and trauma. In relation to other exposures and experiences reported for non-Gulf War military service or civilian occupations, the two groups were similar. Few women in either study group had been on an active deployment other than the Gulf War.

Female Gulf War veterans were similar to male Gulf War veterans in relation to some measures of physical and psychological health. The most common physical symptoms reported by female veterans were often the most common symptoms reported by male Gulf War veterans. Both female and male Gulf War veterans were likely to have heightened recent psychological morbidity compared with their comparison groups. In relation to exposures, female Gulf War veterans were likely to report similar patterns of psychological stressors and immunisations, higher exposure to SMOIL and pesticides and lower exposures to solvents, fuels, engine exhausts and dust, compared with male Gulf War veterans.

16. Reproductive health outcomes

16.1 Aim

The aim of this analysis is to investigate whether male Australian Gulf War veterans report higher than expected adverse reproductive outcomes, or adverse health outcomes in their live children, following the period of the Gulf War.

16.2 Research questions

1. Is there an increased risk of fertility difficulties in Australian Gulf War veterans following the period of the Gulf War?

2. Is there an increased risk of miscarriage, stillbirth or termination amongst pregnancies fathered by male Gulf War veterans following the period of the Gulf War?

3. Are the children of male Gulf War veterans, born after the period of the Gulf War, at greater risk of being born prematurely, having a low birth weight, having a cancer, having a birth defect or dying?

16.3 Methods and materials

Questions relating to fertility difficulties, reproductive outcomes and the health of live children were included in the postal questionnaire.

Fertility difficulties were defined as difficulties getting pregnant or fathering a pregnancy despite trying for at least 12 months. The year that these difficulties began was reported. Participants were asked whether they had sought or undertaken infertility treatment, whether a cause for the fertility difficulties had been found and whether they had since become pregnant or fathered a pregnancy.

For all fathered pregnancies for all participants (irrespective of fertility status), subjects were asked to report whether the pregnancy resulted in a live birth, miscarriage, stillbirth or termination and to provide the date for each of these outcomes. Participants were not asked to provide reasons or causes for miscarriage, stillbirth or terminations. In relation to live births, study participants were asked to report birth weight and duration of pregnancy. Participants were also asked to report whether any live born child had a cancer, birth defect or chromosomal abnormality or other serious health problem and to identify these. Further, participants were also asked to report whether any live born child had subsequently died and the reason for this.

Reported birth defects and chromosomal abnormalities were screened by the study team and excluded if they were clearly misclassified. Reports of ‘other serious health problems’ were also reviewed by the study team. Some of these health problems were identified as probable birth defects and were included as such.

Birth weights were categorised as “low birth weight” if reported to be < 2500 grams. Of those categorised as “low birth weight”, some were further categorised as “very low birth weight” if reported to be < 1500 grams.

Births were categorised as “premature” if the term of pregnancy was reported to be ≤ 36 weeks.

Reported cancers were checked against the records of the National Cancer Statistics Clearing House (NCSCH) when sufficient information was given regarding the identity of the child and when consent was provided for matching the information with the NCSCH.

To identify those outcomes most likely to have occurred in the period following the Gulf War, fertility difficulties and adverse reproductive outcomes reported as occurring in 1991 or later were identified. Further, the health of live children was assessed and reported only for those born in 1992 or later.

16.4 Results

Reproductive health outcomes were assessed for all 1424 Gulf War veterans and 1548 comparison group subjects who completed the study postal questionnaire. However, there were some missing data for various items within the reproductive health section of the questionnaire, and therefore the total number of participants contributing information varies within the tables presented below.

16.4.1 Fertility difficulties

In total, approximately 14% of Gulf War veterans and 13% of the comparison group reported fertility difficulties in their lifetime. In Table 16.1 these are divided in to those who reported first experiencing fertility difficulties prior to 1991, and those who reported first experiencing fertility difficulties in 1991 or later. Gulf War veterans were no more likely than the comparison group to have reported experiencing fertility difficulties prior to 1991, but more likely to have reported these occurring for the first time in the period 1991 or later. Of those subjects in both groups who reported fertility difficulties in the period 1991 or later, approximately half had sought infertility treatment and, of these, more than half had found causes for their fertility difficulties. Gulf War veterans who reported fertility difficulties in the period 1991 or later, were more likely than comparison group subjects to report that they had since fathered a child.

Table 16.1 Self-reported fertility difficulties

	GWV		Comp grp					
	n	**(%)**	**n**	**(%)**	**Crude OR**	**Adj OR**	**95% CI**	**P value**
	N=1378		N=1504					
Experienced difficulty getting pregnant pre-1991	65	(4.7)	92	(6.1)	1.1	-	-	-
	N=1313*		N=1412*					
First experienced difficulties in 1991 or later	130	(9.9)	102	(7.2)	1.4	1.4	1.0-1.8	0.032
Sought infertility treatment	53	(4.0)	47	(3.3)	1.2	1.2	0.8-1.8	0.406
Cause for infertility found	31	(2.4)	25	(1.8)	1.3	1.2	0.7-2.1	0.431
Fathered a pregnancy since then	85	(6.5)	52	(3.7)	1.8	1.8	1.3-2.6	0.001

* Persons reporting fertility difficulties prior to 1991 are excluded.

16.4.2 Pregnancy outcomes

Live births, miscarriages, stillbirths and terminations reported to have occurred in 1991 or later are shown in Table 16.2. The pattern of these pregnancy outcomes in the two study groups is very similar. Live births were the outcome for more than 80% of pregnancies in each group. Still births and miscarriages combined represented approximately 14% of the pregnancy outcomes in both groups and terminations represented just under 5% of the pregnancy outcomes in both groups.

The 1170 and 1272 live births were reported by 684 Gulf War veterans (48%) and 732 comparison group subjects (47%) (data not shown). These two groups both reported an average of 1.7 live births.

Table 16.2 Self-reported pregnancy outcomes in 1991 or later

	GWV		Comp grp					
Pregnancy outcomes in 1991 or later	**n**	**(%)***	**n**	**(%)***	**Crude OR†**	**Adj OR**	**95% CI†**	**P value‡**
Number of pregnancies	N=1448		N=1555					
Live births	1170	(80.8)	1272	(81.8)	-	-	-	-
Miscarriages	204	(14.1)	197	(12.7)	1.1	1.1	0.8-1.3	0.709
Stillbirths	5	(0.4)	14	(0.9)				
Terminations	69	(4.8)	72	(4.6)	1.0	1.0	0.7-1.5	0.960

* All percentage values are derived from N=1448 pregnancies in the Gulf War veterans column and N=1555 pregnancies in the comparison group column.
† Odds ratios are for miscarriages/stillbirths or terminations compared to live births. Odds ratios obtained by polytomous logistic regression adjusting for age, rank, service type, education, marital status, smoking and alcohol.
‡ CI and P values are adjusted for clustering of multiple pregnancies within individuals.

16.4.3 Health of live born children

Health related outcomes for children born in 1992 or later are shown in Table 16.3.

Table 16.3 Reported outcomes for children born in 1992 or later

	Gulf War veterans		Comp. group					
Children born in 1992 onwards	**n**	**(%)**	**n**	**(%)**	**Crude OR**	**Adj OR**	**95% CI‡**	**P value‡**
Number of children	N=1096	-	N=1145	-				
Low birth weight	56	(6.3)*	65	(6.9)*	0.9	0.9	0.6-1.3	0.503
Very low birth weight	9	(1.0)*	9	(1.0)*	1.1	1.0	0.4-2.8	0.992
Premature birth	71	(7.3)†	94	(9.4)†	0.8	0.7	0.5-1.1	0.097
Reported cancer	4	(0.4)	1	(0.1)	4.2	-§	0.5-38.0	0.196
Reported birth defect	40	(3.6)	38	(3.3)	1.1	1.0	0.6-1.6	0.967
Reported death	2	(0.2)	4	(0.3)	0.5	-§	0.1-2.9	0.463

* These percentages are derived from N= 885 live births for Gulf War veterans and N= 936 live births for the comparison group for whom birth weight was provided.
† These percentages are derived from N= 978 live births for Gulf War veterans and N= 997 live births for the comparison group for whom duration of pregnancy was provided.
‡ Standard errors adjusted for clustering of multiple births within the same individual.
§ Due to the small numbers of events, this odds ratio adjusting for confounders and clustering was not computed. The associated 95% CI is for the crude odds ratio adjusted for clustering.

The 1096 and 1145 live births were reported by 665 Gulf War veterans (47%) and 687 comparison group subjects (44%). The children in both study groups were reported to have a very similar pattern of birth weight and duration of gestation and a very similar pattern of birth defects. The quality of the self-reported birth defect data was not high enough to confidently categorise the birth defects into major or minor congenital defects. The total numbers of cancers and deaths were very small in both groups.

16.4.4 Validation of reports of children with cancer

The validation of reports of children with cancer included all children regardless of their year of birth. In total, Gulf War veterans reported six children with cancer and the comparison group reported eight children with cancer.

One comparison group subject did not give consent for his child's details to be matched with the NCSCH. Therefore the identification details for the six Gulf War children, and for seven of the comparison group children, were sent to the Australian Institute of Health and Welfare (AIHW) for matching with the NCSCH.

The NCSCH confirmed cancers in five of the six Gulf War children, and in four of the seven comparison group children.

Of the four Gulf War children born in 1992 or later and reported to have cancer, three were confirmed by the NCSCH match. The one comparison group child born in 1992 or later and reported to have a cancer, was not confirmed by the NCSCH match.

16.5 Discussion

Gulf War veterans reported more fertility difficulties than the comparison group in the period following the Gulf War, but this group also reported greater success in subsequently fathering a child. The two study groups reported similar rates of pregnancies and live births in the period since the Gulf War, and there appear to be no apparent differences in the risk of still births, miscarriages or terminations reported for that time period. Similarly, there appear to be no differences in risk of birth defects or congenital malformations reported between the two study groups. The numbers of reported cancers and deaths in children were too few in both groups to be meaningfully interpreted.

Using a similar, though stricter definition for fertility difficulties, a study of Western Australian couples reported the prevalence of lifetime 'infertility' to be approximately 19%;[392] 5%-6% higher than that reported by both of our study groups. In comparison with self reported data from US Gulf War veterans,[239] Australian Gulf War veterans reported similar live birth-to-pregnancy ratios but lower rates of still births, premature birth and birth defects. When compared with US Gulf War veteran data collected from birth registries,[190, 191] Australian veterans have similar or lower rates of low birth weight, premature birth and birth defects. There are few other sources of comparable data on infertility and other reproductive outcomes in the Australian population or international Gulf War populations.

All findings in relation to reproductive health outcomes in this study should be interpreted with some caution. The numbers of adverse reproductive outcomes reported by the study groups for the period following the Gulf War are quite small, limiting the power of the study to identify small differences in risk. The conclusions are also limited by the study's primary reliance on self-reported data, an inability to directly assess the female partners of study participants, an inability to control for various genetic, health and psychosocial factors

involved in fertility and reproductive outcomes and a paucity of comparable Australian normative data.

The self-reported data, provided in relation to reproductive outcomes in this study, was often only partially complete. Many participants did not provide clear information about dates of pregnancy outcomes or types of cancers or birth defects. Even after thorough follow-up attempts to re-contact study participants about missing data, there often remained large numbers of cases where the information provided was of insufficient quality to be included in the study results.

Large US studies on birth defects in children of Gulf War veterans have shown differing results depending on whether the data was self-reported or collected from medical records or birth defect registries. The self-reported data collected by Kang *et al*[239] showed an increased risk of birth defects associated with Gulf War service, whereas Cowan *et al*[190] and Araneta *et al*[191] found no increased risk when data was drawn from medical records and birth defect registries. Kang *et al* concluded that there was some over reporting of birth defects in both study groups, possibly because the study did not predefine or provide examples of birth defects. The rate of over reporting, however, was assessed to be slightly higher in the Gulf War veterans group.[239]

Self reported information about reproductive outcomes has been shown to be poorer in men than in women. A study of 857 US couples concluded that husbands substantially misreported their wives reproductive histories.[393] The couples only recorded 88.5% agreement on numbers and dates of live births. Men were shown to misreport the prevalence of low birth weight (sensitivity 74%), spontaneous abortion (sensitivity 71%) and induced abortion (sensitivity 35%). The quality of the reproductive health data provided by male participants in our study is unknown, however it is unlikely misreporting of this nature would be different between Gulf War veteran males and comparison group males. The extent to which male participants sought the advice of their female partners when completing the reproductive history section of the postal questionnaire is also unknown.

Whilst our study attempted to validate self-reported cancers in children of study participants, this included only five children born following the period of the Gulf War, of which three cancers were confirmed. Where cancers were not confirmed, reasons for this could include insufficient information about the child's name, date of birth, subsequent change of name, State and date of diagnosis. The diagnosis could have been too recent to be found in the NCSCH which, at the time of matching, only held data on known cancers to the end of 1998. In general, cancers reported in children of Gulf War veterans were more likely to be confirmed than cancers reported in children of the comparison group, implying that Gulf War veterans are not over reporting this health outcome.

Similar to the findings reported by Kang *et al*[239] some over-reporting of birth defects could be expected in both of our study groups as the postal questionnaire did not pre-define or provide examples of birth defects. Australian national data estimates the rates of birth defects or congenital malformations between 1981 and 1996 to have been 160.1 per 10,000 live births (1.6%),[394] a rate half of that reported by our study groups. However this national data set only included major birth defects. Whilst the study team attempted to identify major birth defects amongst all defects reported, the quality of the self-reported data was too poor for this to be undertaken with certainty. Therefore all self-reported birth defects were included in the results unless they were assessed as being clearly not a birth defect. Our study did not seek medical confirmation of the reports of birth defects.

Multiple factors may contribute to infertility and adverse reproductive health outcomes and these include the age and health of female partners. Other factors include any history of conditions such as endometriosis, pelvic inflammatory disease, disorders of ovulation, early menopause or congenital abnormalities. The inability of the study to collect this type of information substantially limits our ability to compare our results with other studies or to draw firm conclusions about possible differences between the two study groups.

There are other possible avenues of research which would more conclusively assess the risk of adverse reproductive health in Gulf War veterans. Information about female partners could only be effectively sought with a further study of randomly selected participants and their partners. Medical records could be sought and birth defects registers accessed in an attempt to validate birth defects and other adverse reproductive outcomes or health outcomes in children. The process of matching reports with the state-based birth defects registers is complicated and the reported data is probably of insufficient quality to allow this. Further, there is not a central national birth defects register that contains identifying details which can be used, and the various state and territory registers which do exist have not employed a standardised approach to data collection or coding.

16.5.1 Summary of findings

With due consideration of the limitations placed on interpretation of our data, the study can make some general statements in relation to the research questions posed.

Male Gulf War veterans appear to be at slightly greater risk of fertility difficulties following the period of the Gulf War. However, this group is more successful at subsequently fathering a child and the two groups report similar rates of pregnancies and live births.

There appears to be no increased risk of miscarriage, stillbirth or termination amongst pregnancies fathered by male Gulf War veterans following the period of the Gulf War.

Children of male Gulf War veterans, born after the period of the Gulf War, do not appear to be at greater risk of being born prematurely, having a low birth weight or having a birth defect or chromosomal abnormality. The numbers of cancers and deaths in children are too small to make any firm conclusions at this stage, however early indications are that there is no increased risk in the children of Gulf War veterans.

17. Cohort study of mortality and cancer

The Australian Gulf War veterans' Health Study has two major components. The first of these is a cross-sectional study, the findings of which are presented in the previous chapters of this report. The second is a cohort study of mortality and cancer.

This chapter describes the aims, research questions, methods and results for the cohort study of Australian Gulf War veterans and a frequency matched comparison group to determine all-cause mortality and cancer incidence rates using data from the National Death Index (NDI) and the National Cancer Statistics Clearing House (NCSCH). This cohort study covers the time period from 1st January 1991 to 31st December 1998 for the cancer incidence study and from the 1st January 1991 to 31st December 2000 for the mortality study.

The cross-sectional study of this Gulf War veterans' cohort and frequency matched comparison group, which investigates other research questions relating to the health outcomes and to the relationship between any excess risks and relevant exposures experienced in the Gulf, is described in the remainder of this report.

The results of this chapter refer only to the male members of the cohort. The mortality and cancer data for the female members of the cohort (38 Gulf War and 74 comparison group subjects) is reported in the Health of female Gulf War veterans chapter, consistent with the presentation of data on their other health outcomes.

17.1 Aim

The aim of these analyses is to investigate whether male Australian Defence Force personnel who served in the Gulf War have an excess risk of death or of developing cancer.

17.2 Research questions

1. Do Australian Gulf War veterans have a greater rate of death than the Australian community?

2. Do Australian Gulf War veterans have a greater rate of death than the comparison group?

3. Do Australian Gulf War veterans have a greater rate of death from injury than the comparison group?

4. Do Australian Gulf War veterans have a greater risk of developing cancer than the Australian community?

5. Do Australian Gulf War veterans have a greater risk of developing cancer than the comparison group?

17.3 Methods

To answer the research questions of the study, the names and identifying details of the cohort (Gulf War veterans and comparison group) were matched with national mortality and cancer data using data from the NDI and NCSCH at the Australian Institute of Health and Welfare (AIHW). The mortality and cancer experience of the cohort was then compared with that of the Australian population in a process that standardised for the age composition of the cohort.

17.3.1 Cohort composition

The study groups of the cohort for the mortality and cancer study were:

1. Gulf War veteran group: All persons on the Gulf War Nominal Roll except cross-sectional study participants who did not consent to be in the mortality and cancer study.
2. Comparison group: All eligible comparison group subjects except cross-sectional study participants who did not consent to be in the mortality and cancer study.

There were 1833 male Gulf War veterans on the Nominal Roll. None of the cross-sectional study participants declined to be in the mortality and cancer study. The comparison group totalled 2850 male subjects. Only two comparison group cross-sectional study participants did not consent to be in the mortality and cancer study. Therefore, the male cohort for the mortality and cancer study was composed of the:

- Gulf War veteran group, which totalled 1833 and included 1558 Navy, 115 Army and 160 Air Force subjects, and
- comparison group, which totalled 2848 and included 2087 Navy, 319 Army and 442 Air Force subjects.

17.3.2 Registry matching process

17.3.2.1 Matching process

Approval was obtained from the AIHW Ethics Committee and all the State and Territory Cancer Registry Ethics Committees to undertake a search and computer matching of our study group with data held in the NDI and NCSCH. Permission was also obtained for the AIHW to release cause of death and cancer type for subjects for whom a match was made.

The NCSCH receives data from each of the eight State and Territory cancer registries on cancer diagnosed in residents of Australia, commencing with cases first diagnosed in 1982. The NDI is a database, which contains records of all deaths occurring in Australia since 1980. The NDI data are obtained from the Registrars of Births, Deaths and Marriages in each State and Territory.

The NCSCH and NDI databases hold a standard set of identifying information for all Australian cancers and deaths, and their use for epidemiological research allows a very complete coverage of cancers and deaths in the population.[395, 396] State and Territory cancer registries or Registries of Births, Deaths and Marriages supply regular cancer record or death record updates to the NCSCH or NDI respectively. The NCSCH is regularly linked to the NDI, as part of normal NCSCH practices, to assist State and Territory cancer registries to identify deaths occurring interstate or that were not notified to the cancer register.

Cancer status of the cohort was determined using the data of the NCSCH. The study Number and personally identifying variables such as names (1st and 2nd and surname; and other names such as maiden name and aliases where applicable), full date of birth, sex, last known address and state for members of the cohort was supplied to AIHW. After the match, AIHW provided information to confirm that there was a match, all occurrences of cancer for individuals in the match, and site of body (topography), histology, date of diagnosis, and state that the cancer was diagnosed in. To preserve confidentiality once the matching process was complete, the personal identifiers were discarded and subjects were identified by their study number only. Cancer topography was coded according to the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-!0)[307] and cancer histology was coded according to the International Statistical Classification of Diseases for Oncology – 2nd edition (ICD-O).[397]

Deaths were determined using the NDI. The study number and personally identifying variables such as names (1st and 2nd and surname; and other names such as maiden name and aliases where applicable), full date of birth, sex, address, state and other details as required for the matching process to the NDI were supplied to the AIHW. The AIHW supplied identifying information to confirm that there was a match as well as the occurrence, date, cause and place of death. Underlying cause of death was available for records to 1996, and these were coded according to the International Classification of Diseases, 9th revision (ICD-9).[275] Underlying cause of death and all other causes of death mentioned on the death certificate was available for records from 1997-2000, and these were coded according to ICD-10. Codes between 8000 and 9999 were codes for external causes of injury and poisoning (E-codes).

The cohort data were matched against the NDI and NCSCH in July 2002 using a series of passes with different search characteristics each time. The matching between the cohort's data and the NDI and the NCSCH was undertaken using a probabilistic record linkage package called Integrity. Multiple passes, which grouped the data based on different characteristics at each pass (eg date of birth, sex, and names), were used in the matching. Generally each successive pass on the data was slightly more liberal in accepting matches. Pass 1 generally provided exact matches and subsequent passes require some clerical review to ascertain best possible matches. The mortality match was conducted against NDI using date of birth where available in the NDI and estimated year of birth where date of birth was not available in the NDI.

Clerical staff at the AIHW reviewed the possible matches to ensure that the least likely matches were excluded. The files received by the Monash study team consisted of details on pairs of subjects, one being the registered death or cancer and the other being the subject of our study. Two members of the study team then independently reviewed the possible matches to determine which ones we considered matches.

17.3.3 Data analysis and statistics

17.3.3.1 Cohort study periods

The defined period of the cohort mortality study match was deaths occurring from 1st January 1991 to 31st December 2000. Mortality is a measure of the number of deaths due to all causes or to a particular cause during a given period.

The defined period of the cancer incidence study was cancers occurring from 1st January 1991 to 31st December 1998. National cause of cancer data for 1998 were the most recent that were available. Cancer incidence refers to the new occurrences of cancer during a given period of time.

Australian population data for mortality and cancer is available from AIHW for each year. Deaths and cancers that had occurred at any time from 1st January 1991 to 31st December 2000 for deaths and 31st December 1998 for cancers were included in the calculation of standardised mortality ratios and standardised incidence ratios.

17.3.3.2 Calculation of person-years

The time contributed by each cohort member to the cohort, or 'person years',[317] was calculated using the Stata statistical package, version 7 (Stata Corporation, 2001, Stata Statistical Software: release 7.0. Stata Corporation, College Station, Texas) and were placed into subgroups based on calendar year and 5 year age group. For the cancer incidence study, subjects commenced contributing person years from 1st January 1991 and continued until the

end of 1998 or the date of diagnosis of a cancer or their death, whichever came sooner. For the mortality study, subjects commenced contributing person years from 1st January 1991 and continued until the end of 2000 or their death, whichever came sooner.

17.3.3.3 Population cancer and death rates

Cancer and death data for the general Australian population were obtained for comparison purposes with the cohort data. General population incidence data for all causes of cancer, for each 5-year age group and calendar year, were obtained from the AIHW. Data on all deaths and size of the Australian populations was obtained from the Australian Bureau of Statistics (ABS) and mortality rates specific to all-cause mortality for each 5-year age group and calendar year were calculated for standardisation purposes.

17.3.3.4 Calculation of rate ratios, standardised cancer incidence ratio and standardised mortality ratios

The expected numbers of deaths and incident cancers, based on the national figures, were calculated using Stata (Stata Corporation, 2001). This involved multiplying the number of person years in each 5-year age group for each calendar year by the national all-cause mortality or cancer incidence for that age group and year.

The Standardised Mortality Ratio (SMR)[317] for each group was calculated as the total number of observed deaths divided by the total number of expected deaths of all causes.

Similarly, the Standardised Incidence Ratio (SIR)[317] for each group was calculated as the total number of cancers observed divided by the total number of expected cancers of all causes.

In keeping with usual practice, and for ease of presentation, the SMRs and the SIRs have been multiplied by 100, as have the 95% confidence intervals.[318] Values over 100 represent increased risk of death or cancer and values below 100 represent decreased risk of death or cancer. A value of 100 is where the risk of cancer or death is the same as that in the Australian population.

The rate of death or cancer in the Gulf War veteran group was compared with the rate of death or cancer in the comparison group of the cohort using rate ratios (RR). Rate ratios were calculated using Cox regression.[317] Entry time was taken as 1st January 1991, and follow-up concluded at 31st December 2000 for deaths and 31st December 1998 for cancers. The crude rate ratio is essentially the ratio of the crude rates for each group (ie, the number of events divided by number of person years). The adjusted rate ratios were adjusted for service, DVA rank and DVA age using these factors as stratification variables in the Cox regression model.

17.4 Results

17.4.1 Cohort composition

17.4.1.1 Demographic characteristics

The demographic characteristics of the cohort are presented in Table 17.1. The mean age of the Gulf War veteran and comparison groups of the cohort group was very similar {27.1 (SD 6.4) vs 27.5 (SD 6.4) years respectively}. The Gulf War veteran cohort group had a similar age composition, and a relatively greater proportion of Navy and other ranks-non supervisory subjects than the comparison group. The differences in service type and rank reflect the greater oversampling for Army and Air Force in the comparison group. This is described in the Cross-sectional study methods chapter.

Table 17.1 Demographic characteristics of the cohort

Characteristic	N=1833 GWV n	(%)	N=2847* Comp grp n	(%)
Age (years)				
<20	237	12.9	333	11.7
20-24	544	29.7	800	28.1
25-34	846	46.2	1349	47.4
35+	206	11.2	366	12.9
Service type				
Navy	1558	85.0	2087	73.3
Army	115	6.3	319	11.2
Air Force	160	8.7	442	15.5
Rank				
Officer	405	22.1	721	25.3
Other ranks -supervisory	1168	63.7	1676	58.8
Other ranks – non supervisory	260	14.2	451	15.8

* These summary statistics included one additional comparison group subject who died after the Gulf War but before commencement of the time period of the cohort study on 1st January 1991, and is therefore excluded from further analysis of the cohort.

17.4.1.2 Person years of follow-up

Table 17.1 shows the person years for both the cancer incidence study and the mortality study for both study groups. The number of person years was much larger for the comparison group than the Gulf War group because the comparison group cohort was substantially larger than the Gulf War veteran group.

Table 17.2 Person years for the Gulf War veteran and comparison groups

	N=1833 Gulf War veterans	N=2847 Comparison group
Person years for cancer incidence study	14,574	22,656
Person years for mortality study	18,229	28,339

17.4.2 Mortality results

After matching, 144 matches were found. After reviewing the matches, 43 matched pairs were classed as probable/definite matches. Of ten deaths (2 Gulf War veterans and 8 comparison group subjects) that had been reported to the study team by DVA, 7 were not confirmed through the matching process, and 3 (1 Gulf War veteran and 2 comparison group subjects) were matched but with dates of death outside the cohort time period.

There were 43 matched deaths in the cohort between 1st January 1991 and 31st December 2000. Of these 43 deaths, 20 deaths occurred in Gulf War veterans in 18,229 person years and 23 deaths occurred in the comparison group in 28,339 person years.

The mortality of Gulf War veterans (SMR=73) was lower than that of the general population, although the confidence intervals included 100, indicating that this is not a statistically significant finding (Table 17.3). The mortality of the comparison group (SMR=54) was significantly lower than that of the general population.

Table 17.3 All-cause standardised mortality ratio in the Gulf War veteran and comparison groups, 1st January 1991-31st December 2000

	Gulf War veterans				Comparison group			
Cause of death	**Observed**	**Expected**	**SMR**	**95% CI**	**Observed**	**Expected**	**SMR**	**95% CI**
All cause	20	27.3	73	47-114	23	42.8	54	36-81

Gulf War veterans had a higher all-cause mortality (RR=1.4) than the comparison group, although this was not a statistically significant finding (Table 17.4). Disease-related deaths accounted for relatively more deaths in the Gulf War veterans than the comparison group (RR=2.2), but due to the small numbers, the confidence intervals were wide and were not statistically significant (Table 17.4). Gulf War veterans had a similar rate of death (RR=1.1) from external causes as the comparison group. Of the deaths due to external causes, one-third were due to intentional self-harm in both study groups. The numbers of deaths in each of the 'type of external cause' categories were small and need to be interpreted with caution.

Table 17.4 Mortality in the cohort from 1st January 1991 to 31st December 2000

Deaths and major cause of death*	**GWV**	**Comp grp**	**Rate ratio†**	**95% CI**	**P value**
Total	20	23	1.4	0.8-2.7	0.238
All disease-related (ICD9: 001-799 or ICD10 A00-R99)	10	8	2.2	0.8-5.6	0.113
Cancer (ICD9: 140-239 or ICD10: C00-C97)	5	4	-	-	-
All external causes (ICD9: E800-E999 or ICD10: V01-Y89)	10	15	1.1	0.5-2.9	0.853
Intentional self-harm (ICD9: E950-E959 or ICD10: X60-X84)	3	5	-	-	-
Motor vehicle accidents (ICD9: E810-E825 or ICD10: V01-V79)	2	6	-	-	-
Military aircraft accident (ICD9: E841.1 or ICD10: V95)	2	2	-	-	-
Other External Causes	3	2	-	-	-

* Underlying cause of death to 31st December 1996 are coded in ICD-9, and underlying cause of death and all other causes of death mentioned on the death certificate on or after 1st January 1997 are coded in ICD-10.
† Rate ratios were adjusted for age (5-year group), rank, and service type

17.4.3 Cancer results

Following matching, 51 matches were found for the entire cohort. NCSCH staff clerically reviewed these, and 34 pass 1 matched pairs were accepted. One was found to be a duplicate and this was removed. Nineteen of these cancers occurred during the period of the cohort study (1st January 1991 to 31st December 1998). Of the 19 incident cancers, 9 occurred in

Gulf War veterans in 14,574 person years, and 10 occurred in the comparison group in 22,656 person years.

The risk of cancer in Gulf War veterans (SIR=71) is lower than that of the general population, although the confidence intervals include 100, indicating that this is not a statistically significant finding (Table 17.5). The cancer in the comparison group (SIR=50) is significantly lower than that of the general population. There were too few cancers of any particular type to calculate individual SIRs for these.

Table 17.5 All-cause standardised incidence ratios (SIR) in the Gulf War veterans and comparison group, 1910-1998

	Gulf War veterans				Comparison group			
Incident cancers	**Observed**	**Expected**	**SIR**	**95% CI**	**Observed**	**Expected**	**SIR**	**95% CI**
All cancers	9	12.7	71	37-137	10	20.1	50	27-92

Gulf War veterans had a greater rate of cancer than the comparison group (RR=1.5), but this was not a statistically significant finding. There were too few cancers of any one type to calculate the rate ratios for these.

Malignant melanoma and cancers of the digestive organs accounted for similar proportions of cancers in both study groups. However, the numbers were small and need to be interpreted with caution.

Table 17.6 Numbers of cancers and rate ratios in the Gulf War veteran and comparison group - 1991 to end 1998

Cancers and major sites of cancer*	**GWV**	**Comp Grp**	**Rate ratio†**	**95% CI**	**P value**
Total (*ICD10: C00-C97)*	9	10	1.5	0.6-3.9	0.357
Malignant Melanoma (*ICD10: C43-C44)*	3	4	-	-	-
Digestive Organs (*ICD10: C15-C26)*	2	2	-	-	-
Other Sites	4	4	-	-	-

* All cancer sites are coded in ICD-10

† Rate ratios were adjusted for age (5 year group), rank, and service type

17.5 Discussion

In this chapter we report on the cohort study of mortality and cancer in which we compared the all-cause mortality and cancer incidence for male Gulf War veterans with the corresponding rates for a male comparison group matched for age, rank, service type and operational status. We also compared the rates of mortality and cancer in both these groups with the corresponding rates in the general Australian population.

The main findings are that although the Gulf War veterans have had a slightly higher death rate than the comparison group, the numbers are too small at this stage to achieve statistical significance. Disease-related deaths accounted for relatively more deaths, while external causes death rates were similar, in the Gulf War veterans compared with the comparison group. The numbers are small and need to be interpreted with caution. Both Gulf War

veterans and the comparison group have lower numbers of deaths than expected using the general population death rates, although the lower rate is statistically significant only in the comparison group.

The cancer incidence of the Gulf War veterans and the comparison group is also lower than that of the general population, but is also statistically significant only in the comparison group. For both the cancer and death findings, the numbers are too small to compare different types of cancer or causes of death, to look at latent periods and time windows, or to explore Gulf War exposures and experiences.

The results of mortality studies of 53,462 UK Gulf War veterans[193] and 695,516 US Gulf War veterans have previously been reported.[109, 247] These studies involved considerably greater numbers of veterans than in the Australian study, and were able to analyse separately for causes of death and cancer sites, with greater statistical power to detect differences between groups. The US 7 year follow-up study that extended to 31st December 1997 and the UK study that extended to 31st March 1999 were conducted for time periods most comparable to that of our study. Our all-cause mortality results were similar to those of these overseas studies, where male US Gulf War veterans had slightly lower risk,[109] and male UK Gulf War veterans[193] had a similar risk of all-cause mortality compared with their non-Gulf comparison groups.

Mortality from external causes was higher and mortality from disease-related causes was lower in these US and UK Gulf War veteran studies, although the differences were significantly different only for the disease-related causes in US veterans. These findings contrast with our Australian study, which found higher than expected numbers for disease-related deaths, and similar numbers of deaths from external causes when compared with the comparison group. The higher mortality from external causes in the US and UK veterans was primarily due to motor vehicle accidents. The significant excess of deaths due to motor vehicle accidents that was observed in US Gulf War veterans in the early 3-year follow up study;[247] had decreased to levels found in non-Gulf veterans by the 7-year follow up.[109] There was no significant excess of overall cancer deaths or deaths from cancer at any specific site among male US or UK Gulf War veterans compared with non-Gulf veterans. The risk of death for both US Gulf War veterans and non-Gulf veterans remained less than half those expected in the general US population,[109] a finding which is not as marked as in our study. These findings of lower than expected death rates when compared with the general population are similar to those reported in mortality studies of veterans of other conflicts, such as the Vietnam War.[398, 399]

A particular strength of our study of cancer incidence in Gulf War veterans was the access to national cancer registry data, which has very complete national ascertainment of cancer cases. Few countries have complete national cancer registration and therefore, studies in those countries have relied on investigating the cancer experience of Gulf War veterans through studies of hospitalisations[19, 173] and mortality,[109, 192, 193] through the registry referral programs[19] and to a limited extent through cross-sectional studies.[16, 20]

Several factors have been discussed in the international literature in relation to the very low mortality of Gulf War veterans and at times these have resulted in intense debate.[109, 193, 247, 400-403] One example is the 'healthy worker effect', which refers to the fact that workers are on average healthier than the general population. Armed forces personnel are also generally healthier than the general population and even healthier than most of the general working population. This is a result of screening entrance medicals, maintenance of fitness while serving and early discharge from the services if medically unfit. This is referred to as a

'healthy soldier effect' and is a reason why death and cancer rates are usually low in veteran populations when compared against general population data. This is the reason that our study included a comparison group of other service personnel.

Another criticism of previous studies is that the comparison of Gulf War veterans with non-deployed personnel may be subject to a bias known as the 'healthy warrior effect'.[400] This is because service personnel eligible for deployment are likely to be fitter, on average, than service personnel who are in no-operational areas. To address this, all eligible subjects for inclusion in our study, both Gulf War group and comparison group, were eligible for active duty at the time of the Gulf War. Any difference in the risk of mortality or cancer between the two study groups should, therefore, not be attributable to a 'healthy warrior effect'. The numbers of cancers and deaths in Gulf War veterans and comparison group in our study, are too small to assess this further.

One aspect of the mortality study that needs to be considered is the possible non-identification of deaths and the accuracy of the NDI data. During the recruitment process and finalisation of the eligible and recruitable sample sizes (see Recruitment chapter), it was found that a total of 53 of the eligible sample were reportedly deceased according to DVA records, and these persons were excluded from the recruitable sample of the study. Of these, 22 were Gulf War veterans and 31 were comparison group subjects. As part of the cohort mortality study matching process with NDI data, the names of these reportedly deceased subjects were checked against the NDI data. Seven were not matched (one of the Gulf War veteran group and six of the comparison group) in a matching time period that extended from January 1990 to February 2002. There are a number of possible reasons for this, including the level of accuracy of the original information or that of the NDI. Accuracy of the NDI has been estimated at 88.8-95% sensitivity[404, 405] and 98.2% specificity.[405] These data show that the matching process with the NDI data is not a perfect one, with some real deaths not detected and a smaller risk of some false death matches made. If all the DVA reported deaths had been confirmed during the NDI search, the mortality rate ratio would have been reduced from 1.35 to 1.26. Therefore, this would have reduced, but not eliminated, the excess seen in the Gulf War group compared to the comparison group, and would have reduced the impact of the 'healthy worker' mortality effect seen in the comparison group relative to the general population.

Participation bias did not affect the results of our study, as the whole cohort (except the two comparison group subjects who declined to participate in the mortality and cancer study) was matched against the data held by the NCSCH and the NDI.

These searches only included death data up until 9 years after the Gulf War and cancer incidence data up until 7 years after the Gulf War. Diseases of long latency, such as cancer, tend to become evident many years after exposure. Therefore, this analysis is likely to be too early to be able to detect increased risks of long latency diseases following Gulf War service. To determine what numbers would be required to assess the risk of developing such diseases, we performed power calculations[406] for the comparison of death and cancer rates between the Gulf War veterans and comparison group subjects. Based on the current numbers, the calculations indicated that 43 deaths in the combined cohort had 80% power to detect a death rate ratio of approximately 2.4, and a cancer rate ratio of 4.0. To detect a rate ratio of 2.0 with 80% power (for either death or cancer) would require approximately 71 events to be observed in the total cohort, and a rate ratio of 1.5 would require approximately 200 events. These calculations indicate that further follow-up of the total cohort is necessary to detect moderately increased rates of cancer or death.

It should be acknowledged that the cohort is quite small and relatively young, so it was anticipated that there would be low numbers of cancers and deaths and low power to detect excess mortality and cancer rates at this stage. This cohort should be followed prospectively to measure mortality and cancer experience and to monitor other health indicators. In particular, it will be important to see if the current small excesses in cancer incidence and disease-related deaths are maintained over time. Statistical power for this cohort study will increase in the future as the cohort ages, and it is only through further searches being conducted in the future, to monitor the health and causes of death of this cohort, that any excess rates of diseases of long latency, such as cancer, will be detected. This will also allow further analyses of possible risk factors such as service type, rank, and exposures or experiences that occurred in the Gulf to be explored. This was not possible due to the current low numbers of cancers and deaths in the cohort overall.

17.5.1 Summary of findings

1. Australian Gulf War veterans do not have a greater rate of death or risk of cancer than the Australian community at this stage.

2. Australian Gulf War veterans have a slight excess of rate of death and development of cancer than the comparison group, but as the numbers are small at this stage, and the possibility of these being chance findings cannot be excluded.

3. Australian Gulf War veterans do not have a greater rate of death from injury than the comparison group, but there is a slight excess in disease-related deaths at this stage. Again, the numbers are small, and the possibility of this being a chance finding cannot be excluded.

18. Factor analysis of self-reported symptoms

In the General Health chapter 9 it was seen that all self-reported symptoms were more commonly reported in the Gulf War veterans than in the comparison group. However, this does not preclude the co-occurrence of self-reported symptoms being similar in the two groups.

In order to investigate whether the pattern of self-reporting of symptoms was the same between the Gulf War veterans and the comparison group, a statistical technique known as factor analysis was employed. Frequently used for many years by psychological researchers, especially in the fields of intelligence, and personality (eg, Cattell;[407] Eysenck;[408] Spearman[409]) (exploratory) factor analysis refers to a "set of statistical methods for analysing the correlations among several variables in order to estimate the number of fundamental dimensions [factors] that underlie the observed data and to describe and measure those dimensions".[202] More specifically, Cattell[330] defined the purpose of factor analysis as being to "find a new set of variables, fewer in number than the original variables, which express that which is common among the original variables". In the context of this study, factor analysis attempts to determine whether the co-occurrence of self-reported symptoms can be explained by a number of underlying and unobserved dimensions, called factors. An example of the use of this methodology is a study of Gulf War veterans in Iowa, USA, by Doebbeling *et al*,[160] in which they employed a separate exploratory factor analysis for the Gulf War and comparison group subjects.

18.1 Aim

The aim of this chapter is to investigate the pattern of self-reported symptoms of Gulf War veterans in the Symptom Questionnaire and to determine whether there is a unique pattern of such symptom reporting present in the Gulf War veterans that is not also apparent in the comparison group.

18.2 Research questions

1. Can the patterns of self-reported symptoms in Gulf War veterans be explained by a small number of underlying factors?

2. Do the comparison group subjects display similar patterns of self-reported symptoms to those of the Gulf War veterans?

18.3 Methods

The responses to the 63 self-reported symptom questions in the self-reported Symptom Questionnaire comprised the source data for the factor analysis. Each symptom question had possible responses on a four-point scale of none, mild, moderate or severe expression of the symptom during the previous month. As the response scale was of a purely ordinal nature (ie, possible responses are ordered from least to most severe but the points may not be equally spaced and are not assigned numerical scores), factor analytic methods appropriate for ordinal data were employed. The methodology used[410] was implemented in the Mplus software package.[331] In brief, for each symptom, each person is assumed to have a continuous (quantitative) underlying amount of that symptom, and persons with a tendency/amount above a certain threshold will state the symptom as being present. (When considering multiple response categories ie, mild, moderate, severe; there is an additional threshold for each category). These underlying tendencies are assumed to follow a bivariate

Gaussian (ie, normal) distribution. A polychoric correlation[411] is computed by an iterative procedure using the observed ordinal indicators to estimate the correlation between the (unobserved) underlying tendencies/amounts of each pair of individual symptoms. This correlation is employed in preference to the usual Pearson cross-product correlation applied to the observed ordinal symptoms, because the latter tends to underestimate the true correlation between the underlying tendencies.[203]

Prior to computing the polychoric correlations for all pairs of symptoms, the data were screened for symptoms with low prevalence that could make the factor analysis procedures computationally unstable and unreliable. In this process one symptom (seizures in past month) was omitted from further consideration because its prevalence was very low (9 persons in total, 0.3%). Any individuals who were missing any of the remaining 62 symptom responses were also excluded (189/2970=6.4%), leaving 2781 (1322 Gulf War, 1459 comparison group) for analysis. In addition, the computation of polychoric correlation coefficients for pairs of symptoms may be unstable if zero cells are encountered on the diagonal entries in the pairwise cross-tabulations (ie, no individual has that particular combination of reported symptoms). To alleviate this possibility, cross-tabulations of all pairs of symptoms were examined and certain individual symptom categories were combined so as to give either three point or two point scales. In such a fashion expected cell frequencies of at least one in all cells of the resulting tables could be guaranteed. This resulted in 28 symptom items being recoded to three categories, 25 symptom items being recoded to two categories (ie, binary) and 9 symptom items retaining their original four point scale.

Polychoric correlations were computed for the symptom data for Gulf War veterans. Exploratory factor analysis was applied to the resulting correlation matrix and factor solutions extracted using diagonally weighted least squares with a robust covariance matrix and a mean and variance corrected chi-squared statistic.[412] (The use of a diagonal weighting matrix avoids potential problems with the inversion of a large populated weight matrix and the robust variance provides correct standard errors for large samples).

A crucial step in a factor analysis is the determination of the number of factors to retain for rotation to an interpretable solution. This determination employed a combination of the eigenvalues (loosely speaking, the amount of variation accounted for by each factor) of the polychoric correlation matrix, the percentage of the total variance explained by each possible number of factors and the associated scree plot (defined below), the reproducibility of the factors, and the clinical meaningfulness of the factors extracted. Both Varimax (orthogonal,[413]) and Promax (oblique, with tuning constant k=2,[414]) rotations were applied to each factor solution. Orthogonal rotation produces uncorrelated factors, whereas oblique rotation allows for the possibility of factors being correlated with each other, as determined by the data.[330, 415] An arbitrary but conventional threshold of 0.40 for the factor loadings (pattern matrix coefficients) was applied when interpreting and labelling the factors. Only brief descriptive labels were defined, because the labels should not be interpreted as implying any clinical diagnosis. The reproducibility of the factor solution was considered important, because extracting greater than the required number of factors can lead to extraction of "noise" specific to a particular sample, with the resulting factor structure not being replicable in other samples, or even in samples from the same population.[416] To assess reproducibility of the factor solutions, the Gulf War group was split randomly in half. Subsequently two, three and four factor solutions were obtained for each half, and the congruence of the solutions for the two halves assessed via Pearson product-moment and intra-class correlation[417] coefficients. (Pearson correlations assess association; intra-class correlations provide a more direct measure of reproducibility[418]). As the two types of correlation

coefficient produced almost identical results, only the Pearson correlations are reported. These and the above considerations led to the adoption of a three-factor model for the factors underlying the pattern of symptoms among Gulf War veterans (see Results section for details).

Factor scores were computed for each individual for each of the three factors using the iterative factor scoring procedure as implemented in the Mplus software.[331] These scores estimate quantitatively *how much* of each of the three factors each individual possesses, or more technically, the location of each individual on the underlying dimension measured by each factor. The construct validity of the three factor solution was assessed by correlating the three factor scores with the SF-12 Physical and Mental scale scores. Internal consistency of each of the three factors was assessed by computing Cronbach's coefficient alpha[266] based on unit weighting (weights equal to one) for the items with loadings greater than 0.40 in each factor.

To assess whether a similar factor structure was also present in the comparison group, two factor analytic methods were employed. First, an exploratory factor analysis with three factors was obtained for the comparison group using the same methods and rotation as described above for the Gulf War group. Congruence of the factor loadings for each factor was compared between the Gulf War and comparison group via intra-class correlation coefficients. Factor scores were computed for each of the three factors for the comparison group subjects using both the factor solution from the comparison group and also the factor solution obtained from the Gulf War group. These scores were then correlated with each other, with a high correlation providing evidence of similarity of the factor structure underlying the symptom patterns observed in the Gulf War and comparison groups. Similar methodology has been employed in a previous study of Gulf War veterans.[160]

The second method of investigating factor structure similarity involved a more formal assessment of invariance of the three-factor solution across the Gulf War and comparison groups. This was performed by implementing and assessing the goodness-of-fit of a two-group structural equation[203] model. The model for each group contained paths from each of the three factors to each symptom item, and allowed the three factors to be correlated. To enable assessment of the invariance of the factor structure across groups, the loadings of all individual symptom paths, the factor covariance structure, and scale and threshold parameters were constrained to be equal across groups. This constrained model also enabled the difference in the mean *amount* of each of the three factors between the two groups to be computed, and these differences in means were rescaled into units of standard deviations of the factors (ie, effect sizes[419]). The adequacy of the fit of the constrained model to the symptom data was assessed with conventional goodness of fit indices together with recent guidelines for their interpretation.[420]

18.4 Results

18.4.1 Factor analysis of self reported symptoms among Gulf War veterans

Exploratory factor analysis of the 1322 Gulf War veterans with complete data on all 62 symptoms yielded 41.1% of the total variance accounted for by the first (general) factor. The second through fifth factors contributed incremental amounts of 3.3%, 2.7%, 1.9% and 1.7%, yielding 47.1% explained by three factors, and 50.7% by five factors. Examination of the 'scree plot',[330] a plot with eigenvalues on the vertical axis and factor numbers (ie, the first factor extracted, second, third, fourth and so on) on the horizontal axis, exhibited a very large

or dominant first factor with possible minor contributions from a further two factors. The remaining factors appeared to be 'scree', a geological term denoting debris or litter. These diagnostic tools indicate that additional factors beyond three contribute very little to explaining the variance of the patterns of symptom reporting. There were 13 factors with eigenvalues greater than one (Kaiser's criterion or Kaiser-Guttman test), however this criterion typically overestimates the required number of factors in situations with a large number of items.[330] Varimax and Promax (k=2) rotations were applied to the two, three and four factor solutions. The Promax solutions provided more distinct and interpretable factor solutions than did the orthogonal Varimax rotations, and indicated that the underlying factors were moderately correlated (eg, inter-factor correlations for the three factor solution were 0.52, 0.47 and 0.44 between factors 1 and 2, 1 and 3, and 2 and 3, respectively).

The assessment of the reproducibility of two, three and four factor Promax solutions using the two randomly split halves of the Gulf War veteran data indicated that the two and three factor solutions each displayed the consistent dominant symptoms loading on each factor in each split-half. The Pearson correlations between the symptom loadings of the factors across the two split-halves for the two-factor solution were 0.78 and 0.86, and for the three factor solution these were 0.78, 0.85 and 0.66. The four factor solution displayed reproducibility of only two of its factors (correlations 0.71 and 0.73), with the remaining two factors not being defined consistently by dominant symptoms across split-halves (correlations of –0.19 to 0.57 across possible candidate "matches"). As the three-factor solution provided interpretable factors in addition to its amount of explained variance and reproducibility, it was adopted as the best representation of the symptom pattern in Gulf War veterans. The pattern of factor loadings in the total Gulf War veteran sample (n=1322) is displayed in Table 18.1, with the ordering of symptoms in the table determined by the size of the coefficients within each factor.

Table 18.1 Factor loadings (pattern coefficients) x100 among the Gulf War veterans (n=1322)

Symptom	Factor 1 (psychophysiological)	Factor 2 (cognitive)	Factor 3 (arthro-neuro-muscular)
Vomiting	**80**	-11	-10
Nausea	**79**	3	-1
Stomach cramps	**70**	1	1
Diarrhoea	**64**	3	-6
Wheezing	**61**	4	1
Indigestion	**60**	-4	13
Shortness of breath	**58**	14	12
Dry mouth	**54**	19	12
Feeling feverish	**54**	17	15
Swelling of lymph glands	**49**	3	16
Lump in throat	**49**	9	11
Persistent cough	**49**	17	-3
Pain on passing urine	**47**	24	1
Constipation	**45**	16	9
Difficulty speaking	**44**	**46**	2
Dizziness, fainting etc	**44**	30	7

Symptom	Factor 1 (psychophysiological)	Factor 2 (cognitive)	Factor 3 (arthro-neuro-muscular)
Loss of balance or coordination	**44**	35	19
Sore throat	**43**	-1	9
Flatulence/burping	**43**	12	14
Loss control bladder/bowels	**43**	26	-6
Burning in sex organs	**41**	26	8
Skin ulcers	**40**	14	9
Loss of, or decrease in, appetite	**40**	**42**	-2
Loss of concentration	10	**80**	5
Feeling distant from others	11	**78**	-3
Unrefreshed after sleep	-5	**74**	28
Forgetfulness	9	**73**	4
Loss of interest in sex	9	**69**	-2
Sleeping difficulties	3	**69**	16
Avoiding things/situations	20	**69**	5
Feeling jumpy/startled	26	**65**	2
Problems sexual functioning	7	**65**	-1
Distressing dreams	15	**65**	7
Fatigue	1	**65**	30
Irritability	14	**64**	5
Difficulty with right word	17	**59**	9
Feeling disorientated	33	**58**	5
Increased sensitivity to noise	22	**52**	5
Shaking	34	**46**	4
Increased sensitivity to light	29	**43**	11
Increased sensitivity to smells/odours	17	**41**	14
Stiffness in several joints	6	5	**88**
Pain several joints (no swelling/redness)	4	10	**81**
General muscle aches/pains	19	4	**67**
Loss sensation hands/feet	22	18	**48**
Low back pain	15	11	**45**
Tingling/burning hands/feet	24	19	**43**
Ringing in the ears	24	22	20
Rash or skin irritation	22	21	19
Itchy or painful eyes	26	24	18
Night sweats soak sheets	23	36	17
Unintended weight gain >4kg	23	22	17
Chest pain	35	19	17
Toothache	37	1	15
Skin infections	25	15	14
Mouth ulcers	23	7	13
Rapid heart beat	37	33	13
Double vision	27	38	12

Symptom	Factor 1 (psychophysiological)	Factor 2 (cognitive)	Factor 3 (arthro-neuro-muscular)
Intolerance to alcohol	32	37	10
Headaches	30	26	9
Passing urine more often	32	32	9
Unintended weight loss >4kg	34	32	0

Descriptive labels to assist in interpretation (but which do not necessarily reflect clinical diagnoses) are suggested based on the patterns of loadings within each factor. The first factor involves psychophysiological distress and marginally explains 23.7% of the total variance. The second factor involves cognitive symptoms and hence is labelled Cognitive distress; it explains 25.2% of the variance. The third factor involves arthritic, muscular and neurological complaints and is labelled Arthro-neuro-muscular distress; it explains 10.8% of the variance. Due to the correlation between the factors, there is a total overlap of 12.6% in explained variance, divided into an overlap of 7.1% between factors 1 and 2, 2.7% between 1 and 3, and 2.8% between factors 2 and 3.

Validity and reliability considerations

The construct validity of the three factors was assessed by computing the Pearson product-moment correlation between the factor scores computed from the three-factor model and the SF-12 physical and mental health subscales. Table 18.2 presents the resulting correlations.

Table 18.2 Pearson correlations between SF-12 subscale scores and Gulf War veteran symptom factor scores

Scale	Factor 1 (psychophysiological)	Factor 2 (cognitive)	Factor 3 (arthro-neuro-muscular)
SF-12 mental	-0.44	-0.73	-0.31
SF-12 physical	-0.47	-0.37	-0.55

note : the Pearson correlation between SF-12 mental and physical subscale scores was .09

All correlations are moderate to large in magnitude (in the negative direction) and highly statistically significant ($P<0.0001$). Factor 1 has both physiological and psychological components and accordingly correlates moderately with both the physical and mental SF-12 subscales. Factor 2, Cognitive distress, correlates higher with SF-12 mental than physical scales, and Factor 3 is the converse.

Assessment of internal consistency with unit weights applied to items with loadings greater than 0.40 within each factor produced Cronbach's coefficient alphas of 0.85, 0.93 and 0.82 for factors one, two and three respectively, indicating satisfactory internal consistency. Furthermore, no items within the any of the factors were identified as redundant – all item-total correlation were in excess of 0.30 and typically in the 0.50 to 0.60 range. Similarly, the coefficient alphas could not be improved by deleting any item from any factor.

18.4.2 Factor analysis of symptoms in the comparison group

As stated earlier in this chapter, the Gulf War veterans displayed a greater prevalence of self-reported symptoms than the comparison group. However, this does not preclude the *pattern*

of symptom reporting being similar in the two groups. In other words, the factors underlying the co-occurrence of symptoms may be the same for the two groups.

An exploratory factor analysis in the comparison group subjects using the same methodology as for the Gulf War veterans (ie, number of factors retained, rotation method) produced a three-factor solution very similar to that in the Gulf War veterans. These results are presented in Table 1.3, where the Gulf War veterans' results are repeated for convenient reference. The inter-factor correlations for the comparison group were 0.48, 0.43 and 0.49 between factors 1 and 2, 1 and 3, and 2 and 3, respectively. The eigenvalues and scree plots for the comparison group subjects were virtually identical to those of the Gulf War veteran data. The intra-class correlations between the factor loadings of each factor between the two groups were 0.94, 0.95 and 0.92 for factors one, two and three respectively, indicating substantial similarity of factor structure. The factor scores computed for the comparison group subjects were likewise extremely similar to the scores for these subjects computed using the Gulf War factor analysis solution, with intra-class correlations of 0.98, 0.98 and 0.99 for factors one, two and three respectively.

Table 18.3 Factor loadings (pattern coefficients) x100 among the Gulf War veterans (n=1322) and comparison group subjects (n=1459)

	Gulf War			**Comparison group**		
Symptom	**Factor 1**	**Factor 2**	**Factor 3**	**Factor 1**	**Factor 2**	**Factor 3**
Vomiting	**80**	-11	-10	**81**	-8	11
Nausea	**79**	3	-1	**67**	19	-4
stomach cramps	**70**	1	1	**51**	11	11
Diarrhoea	**64**	3	-6	**58**	7	-2
Wheezing	**61**	4	1	**61**	-4	2
Indigestion	**60**	-4	13	**40**	12	14
shortness of breath	**58**	14	12	**46**	18	15
dry mouth	**54**	19	12	**48**	22	1
feeling feverish	**54**	17	15	**67**	13	8
swelling of lymph glands	**49**	3	16	**51**	2	15
lump in throat	**49**	9	11	**56**	-11	10
persistent cough	**49**	17	-3	**61**	-9	0
pain on passing urine	**47**	24	1	31	29	9
Constipation	**45**	16	9	21	21	12
difficulty speaking	**44**	**46**	2	27	**49**	-2
dizziness, fainting etc	**44**	30	7	39	35	8
loss of balance or coordination	**44**	35	19	39	**43**	14
sore throat	**43**	-1	9	**51**	-4	-1
flatulence/burping	**43**	12	14	31	14	16
loss control bladder/bowels	**43**	26	-6	38	32	21
burning in sex organs	**41**	26	8	31	**40**	15
skin ulcers	**40**	14	9	**51**	17	6
loss of, or decrease in, appetite	**40**	**42**	-2	**46**	37	-3
loss of concentration	10	**80**	5	12	**79**	3
feeling distant from others	11	**78**	-3	8	**81**	-5

	Gulf War			Comparison group		
Symptom	**Factor 1**	**Factor 2**	**Factor 3**	**Factor 1**	**Factor 2**	**Factor 3**
unrefreshed after sleep	-5	**74**	28	-17	**79**	25
Forgetfulness	9	**73**	4	15	**71**	-2
loss of interest in sex	9	**69**	-2	12	**55**	13
sleeping diff	3	**69**	16	-12	**71**	24
avoiding things/situations	20	**69**	5	9	**72**	9
feeling jumpy/startled	26	**65**	2	13	**65**	6
problems sexual functioning	7	**65**	-1	15	**51**	20
distressing dreams	15	**65**	7	19	**61**	3
Fatigue	1	**65**	30	-4	**68**	22
Irritability	14	**64**	5	8	**63**	9
difficulty with right word	17	**59**	9	19	**64**	-2
feeling disorientated	33	**58**	5	38	**59**	-4
increased sensitivity to noise	22	**52**	5	32	**42**	13
Shaking	34	**46**	4	30	39	11
increased sensitivity to light	29	**43**	11	40	31	9
increased sens smells/odours	17	**41**	14	24	**42**	9
stiffness in several joints	6	5	**88**	6	-1	**91**
pain several joints (no swell, red)	4	10	**81**	2	2	**84**
general muscle aches/pains	19	4	**67**	9	14	**60**
loss sensation hands/feet	22	18	**48**	27	11	**52**
low back pain	15	11	**45**	3	13	**56**
tingling/burning hands/feet	24	19	**43**	26	15	**43**
ringing in the ears	24	22	20	14	21	28
rash or skin irritation	22	21	19	26	11	18
itchy or painful eyes	26	24	18	28	19	20
night sweats soak sheets	23	36	17	34	33	19
unintended weight gain >4kg	23	22	17	15	31	16
chest pain	35	19	17	35	18	23
Toothache	37	1	15	26	12	10
skin infections	25	15	14	24	9	25
mouth ulcers	23	7	13	21	2	13
rapid heart beat	37	33	13	37	33	5
double vision	27	38	12	34	34	1
intolerance to alcohol	32	37	10	26	**41**	6
Headaches	30	26	9	22	27	16
passing urine more often	32	32	9	35	25	14
unintended weight loss >4kg	34	32	0	30	**40**	-17

note : the label given to Factor 1 is psychophysiological distress; that for Factor 2 is cognitive distress : that for Factor 3 is arthro-neuro-muscular distress

The assessment of the adequacy of the fit of the two-group constrained structural equation model used the following indices (with abbreviations and recommended thresholds for adequate fit[420] Tucker-Lewis Index (TLI, >0.95), comparative fit index (CFI, >0.95); root

mean squared error of approximation (RMSEA<0.06) and standardised root mean squared residual (SRMR<0.08). The results displayed an adequate fit of this model (TLI=0.98, CFI=0.98, RMSEA=0.033, SRMR=0.071). The estimated difference in the mean amount of each of the three factors between the Gulf War and comparison groups, expressed in units of effect size, were 0.32 (psychophysiological), 0.40 (cognitive), and 0.16 (arthro-neuro-muscular), all P<0.003. (Cohen[419] defines a medium effect size as 0.50, and a small effect size as 0.20). For all three factors, the Gulf War veterans displayed higher scores (more severe levels of each factor) than the comparison group.

18.5 Discussion

A reproducible factor solution with three moderately correlated factors was identified for the latent structure underlying the pattern of symptom reporting among Gulf War veterans. The three factors also displayed evidence of construct validity and internal consistency. A similar three-factor solution was found for the comparison group subjects. This suggests that the underlying factors affecting symptom reporting patterns in the Gulf War veterans are unlikely to be different to that of the comparison group subjects. This finding does not support the existence of a unique pattern of symptoms affecting Gulf War veterans only, and is consistent with the results of five of the six international studies of Gulf War veterans in which a comparison group was used in the research design.[154, 157, 160, 194, 421] One other study[46] reported similar three, four and five factor solutions between Gulf War and comparison groups, but discovered (and concluded) a difference in the composition of one factor in their six factor solution - a conclusion disputed by the Editor of the journal, in a footnote to the article.

The three factors identified in the Gulf War and comparison group subjects in this study are labelled as psychophysiological distress, cognitive distress and arthro-neuro-muscular distress. These factors display some similarity with those from each of the previous eight studies (six with a control group;[46, 154, 157, 160, 194, 421] and two without a control group,[73, 158]). Exact comparisons involving these studies are difficult because of the use of different lists of symptoms and different factor analytic methods. Of the three factors, the cognitive distress factor is the most reproducible across studies, with seven of the eight studies producing a similar factor. Most studies have also produced either a musculoskeletal factor or a neurological factor, with one study[158] also reporting a combination factor similar to that in this study. Other studies have reported various somatic factors similar to components of the psychophysiological factor produced in this study. The recent report by Shapiro *et al.*, (2002)[421] provides a convenient summary of the methodology, results and factors identified in six of the eight previous studies. More details on the previous studies have been presented in the Review of Health Studies chapter.

The analysis of self-reported symptoms in the General Health chapter indicated increased prevalences for all 62 symptoms among Gulf War veterans relative to comparison group subjects. The two-group structural equation model in this chapter identified three factors underlying these symptoms, with the Gulf War veterans possessing statistically significant elevated *amounts* of each of these three factors. According to the factor analysis model, the elevated amounts are postulated to explain the increased symptom prevalences in Gulf War veterans, albeit with reservations about inferring causal relationships from purely correlational data.

Seven of the eight previous studies employed symptom questionnaires using an ordinal or binary scale for each symptom item. The factor analytic methodology employed varied

between these studies, however none of the seven studies used factor analytic methods which have been developed specifically for ordinal or binary data (although one study,[154] did use such methods in unpublished work and reached essentially the same conclusion as their published work (personal communication, 2002)). The effect of treating ordinal data as interval and using Pearson product-moment rather than polychoric (or tetrachoric for binary symptoms) correlation coefficients is that correlations tend to be attenuated, with the resulting symptom correlation matrix possibly not accurately reflecting the underlying factor structure.[203] Performing an exploratory principal factor analysis on the Gulf War veteran data in this study and treating the ordinal data as interval produced attenuated correlation coefficients as expected. Despite this, three very similar factors to that presented in this chapter emerged from the Promax rotated solution, however the explained variance from the three factors was reduced (28%), and the factor loadings were also reduced.

Factor analysis involves a number of subjective decisions, (eg, number of factors to retain, rotation method, etc), as detailed in the Methods section of this chapter. Other potential limitations of the factor analysis presented in this chapter pertain to non-participation bias among the comparison group subjects, and information bias among Gulf War veterans. It is possible, although purely speculative, that the pattern of symptom reporting among comparison group non-participants differs from that of participants, in which case differences in the underlying factor structure of Gulf War veterans and comparison group subjects may arise. It is also possible that the media coverage given to the health problems of Gulf War veterans may have influenced their patterns of symptom reporting. However, the finding that the comparison group exhibited a very similar pattern of reporting does not support this possibility. It appears more likely that the information bias may only be affecting the *frequency* rather than the *pattern* of symptom reporting, with the differences in the mean levels of the three underlying factors possibly being distorted rather than the underlying factor structure itself.

18.5.1 Summary of findings

In summary, the pattern of symptom reporting among Gulf War veterans is similar to the pattern observed among comparison group subjects. This finding, as is the case with previous studies, casts doubt over the existence of a unique symptom complex affecting Gulf War veterans. However, as is noted by Ferguson[205] the existence (or lack) of a unique underlying syndrome cannot be determined from the factor analysis of self-reported symptoms alone.

For example, two different underlying conditions may produce similar symptoms. Although symptom reporting patterns were found to be similar, the results in this chapter also support the substantive finding presented in the General Health chapter 9 of this report of an increased frequency of self-reported illness among Gulf War veterans.

19. Overall findings, discussion and recommendations

19.1 Introduction and research questions

The Australian Gulf War Veterans' Health Study was prompted by several factors. These include:

- the results of several overseas studies, which had shown that the Gulf War veterans from coalition partner countries were reporting poorer than expected health,
- an increasing number of reports among Australian Gulf War veterans of a wide range of medical problems, which were difficult to explain,
- concern amongst Gulf War veterans about the possible health effects of some of the exposures and experiences unique to the Gulf War, such as smoke and oil from burning oil wells (SMOIL), exposure to depleted uranium and the possible use of chemical or biological weapons.

In response to these factors, the Australian study was designed to investigate whether Australian Defence Force personnel who served in the Gulf War have a higher than expected rate of several adverse physical and psychological health effects and, if so, whether these effects are associated with exposures and experiences that occurred in the Gulf War. The specific research questions were:

1. Do Australian Gulf War veterans have an increased risk of psychological disorders including depression, anxiety and substance disorders and, if so, are these associated with exposures and experiences that occurred in the Gulf War?

2. Do Australian Gulf War veterans have increased prevalences of symptoms, symptom clusters and medical conditions, related to several body systems; in particular psychological, respiratory, neurological, musculoskeletal and skin and, if so, are these associated with exposures and experiences that occurred in the Gulf War?

3. Do Australian Gulf War veterans have an increased prevalence of chronic fatigue syndrome and, if so, is this associated with exposures and experiences that occurred in the Gulf War?

4. Do Australian Gulf War veterans have significantly poorer lung function than expected and, if so, is this associated with exposures and experiences that occurred in the Gulf War?

5. Do Australian Gulf War veterans have an increased prevalence of laboratory test results that are indicative of adverse health effects, including evidence of increased rates of markers of infection; and if so, are these associated with exposures and experiences that occurred in the Gulf War?

6. Do Australian Gulf War veterans have increased risk of having a child with a major congenital malformation, a child who later develops cancer or an increased risk of fertility difficulties, following return from the Gulf? If so, are these associated with exposures and experiences that occurred in the Gulf War?

7. Do Australian Gulf War veterans have increased rates of mortality and cancer?

19.2 Main findings

Each of these main research questions had several components, each of which has been addressed in the specific results chapters. In each results chapter, we have presented and discussed the main findings before drawing conclusions in relation to the research questions relevant to that chapter. The major findings in relation to the main research questions outlined above can be summarised as follows for male Gulf War veterans:

- Australian Gulf War veterans have an increased risk of psychological disorders including depression, anxiety, posttraumatic stress disorder and substance use disorders in the post Gulf War period and persisting within the previous 12 months. These psychological disorders are strongly associated with reported military service experiences that occurred in the Gulf War, especially the threat of attack.
- Australian Gulf War veterans have increased rates of reporting of all symptoms, and some medical conditions; in particular musculoskeletal, psychological, skin, respiratory and neurological conditions and these are associated with several reported exposures and experiences that occurred in the Gulf War. These include immunisations (especially where 10 or more were reported), pyridostigmine bromide and being in an area where chemical weapons had been used.
- While the level of symptom reporting among Gulf War veterans is higher than that in the comparison group, the pattern of symptom reporting in the two groups is similar, with three similar factors identified in each group. This suggests that Gulf War veterans do not have a unique symptom complex or cluster.
- Australian Gulf War veterans do not have poorer physical health than the comparison group, as assessed by physical measurements such as body mass index, waist–hip ratio, blood pressure or fitness on a step test.
- Australian Gulf War veterans have an increased risk of chronic fatigue syndrome, but the numbers are very small (11 Gulf War veterans and 2 comparison group subjects), and are too few to investigate further the role of Gulf War exposures and experiences. In addition, Gulf War veterans report all other fatigue-related health outcomes more commonly than the comparison group. The immunological profile of Gulf War veterans with chronic fatigue syndrome differs on one B cell lymphocyte subset marker to that of the comparison group with chronic fatigue syndrome, but the numbers are small and need to be interpreted with caution. The clinical significance of this finding is uncertain.
- Australian Gulf War veterans have increased rates of reporting of respiratory symptoms, increased rates of asthma according to the European Community Respiratory Health Survey definition (but not increased rates of other respiratory medical conditions), and increased rates of wheeze on physical examination. Gulf War veterans do not have poorer lung function than the comparison group based on the spirometry measures used in this study. The increased symptom reporting and the lung flow indices are not consistently associated with relevant exposures in the Gulf War such as SMOIL or dust storms.
- Australian Gulf War veterans do not have an increased risk of laboratory test results that are indicative of adverse health effects such as anaemia, inflammation, liver disease, raised blood glucose, or increased markers of infection. A greater proportion of Gulf War veterans have increased sodium and creatinine concentration relative to the laboratory reference ranges, suggesting renal disease. However, the number of those affected is very small and the clinical significance of this finding is uncertain, so the results must be interpreted with caution. As no excess risks were found in Gulf War veterans for almost

all laboratory findings, associations with exposures and experiences that occurred in the Gulf War were not explored further.

- Australian Gulf War veterans do not have increased risk of having a child with a congenital malformation or, at this stage, a child who later develops cancer. While there is a small increase in reported fertility difficulties, following return from the Gulf War, veterans with these difficulties are more likely than the comparison group to subsequently father a successful pregnancy. Pregnancies fathered by an Australian Gulf War veteran are not at increased risk of resulting in a miscarriage, stillbirth, prematurity or low birth weight. As no excess risks were found in Gulf War veterans, associations with exposures and experiences that occurred in the Gulf War were not explored further.
- Australian Gulf War veterans, and the comparison group, have substantially lower rates of mortality and cancer, when compared with the Australian population. For the Gulf War veterans, when compared to the comparison group, there is some indication of an increased rate of death due to disease-related causes, while there is a similar rate of death due to external causes. However, the number of deaths from disease at this stage is too small to make any meaningful conclusions in relation to this finding. When Gulf War veterans are compared against the comparison group, they have similar rates of cancer, at this stage

Only 38 female Australian Gulf War veterans took part in the study, which was 84% of those who served there. This small number meant that there was limited statistical power for the analysis of this group. However, a similar, but less marked, pattern in relation to adverse psychological outcomes as for male Gulf War veterans was found. No firm conclusions can be made about any of the other physical health indicators studied, due to the very small numbers of female Gulf War veterans.

Therefore, in response to the main hypothesis of the study we conclude that the health of Australian veterans of the Gulf War does differ significantly from similar Australian Defence Force personnel who were not deployed to the Gulf War. The differences in health outcome are evident across a number of different psychological and physical health outcomes and body systems.

19.3 Discussion

The purpose of the remainder of this chapter is not to revisit the more detailed discussions about the above findings in relation to the research questions. For further discussion of the conclusions reached above, please refer to the relevant chapters of this report. Instead, our aim here is to try to draw together consistent threads in the findings of the study across the different disorders, to compare the strength of the evidence for the different findings, and to look at strengths and limitations of the study as a whole. On the basis of this, we can then make some recommendations from the findings, and highlight some further avenues for research.

Looking at the results as a whole, the most striking and consistent finding is that the Gulf War veteran group has developed more psychological disorders than the comparison group in the time since the Gulf War. In addition, the Gulf War veteran group was more likely to report persisting psychological symptomatology from these disorders within the twelve month period prior to the study. The greatest increase in risk was for anxiety disorders including posttraumatic stress disorder (PTSD), but other disorders including depression and substance use disorders were also more common in the Gulf War group.

There were several factors in the psychological disorder findings that add weight to the conclusion that Gulf War service is related to an increased risk of psychological disorders:

- Firstly, among Gulf War veterans, the risk of these psychological disorders increased sharply as the number of reported adverse experiences related to the Gulf War, as measured by a Military Service Experience questionnaire, increased. This finding indicates a strong dose-response relationship between stresses in the Gulf War and subsequent psychopathology.
- Secondly, the increased risk of psychological disorders persisted, although at a slightly lower level, when the Gulf War veterans were compared just with those comparison group subjects who had been on an active deployment. This indicates that the increased risk of psychological disorders was not just related to deployment in general, but was specific to the Gulf War.
- Thirdly, multiple measures of the same psychological disorders, such as the psychologist administered Composite International Diagnostic Interview (CIDI) module for PTSD and the self administered Posttraumatic Stress Disorder Checklist – S (PCL-S) instrument, produced consistent results for PTSD, although the magnitude of the risk varied.
- Fourthly, many of the symptoms reported more commonly by Gulf War veterans in the general symptom questionnaire were neuropsychological in nature and reported PTSD diagnosis in the medical conditions part of the analysis was found in excess in the Gulf War veteran group.
- Finally, there was also some consistency in the results for male and female Gulf War veterans when considered separately, despite the small numbers in the female Gulf War veteran group.

Although the psychological disorder findings were prominent and the most consistent findings, there were several other important findings in relation to physical health. One major finding was that Gulf War veterans had much higher reporting of general physical health symptoms than the comparison group, especially musculoskeletal symptoms. The Gulf War veterans were more likely than the comparison group to report these symptoms as being moderate or severe in nature.

Somatic psychological disorders can be associated with increased physical symptom reporting with no organic basis. This was examined in our study as a possible reason for the increased symptom reporting, but it is unlikely that the increased physical symptom reporting found in our study is due to a somatic disorder, as these were diagnosed in a very small number of Gulf War veterans (n=18). In addition, no Gulf War veteran was specifically diagnosed with somatisation disorder.

When the increased symptom reporting was examined further using factor analysis, to identify patterns of grouped symptoms, three factors, or groups of symptoms, were identified; psychophysiological, cognitive and arthro-neuro-muscular. However, these three factors were very similar in the two study groups, suggesting that there was no unique pattern of symptom reporting in Gulf War veterans. The Gulf War veterans had elevated amounts of these three factors, however, compared with the comparison group. This is consistent with the findings of some previous overseas studies.

Gulf War veterans self-reported many individual medical conditions that were first diagnosed or treated in 1991 or later, ie after the Gulf War, more frequently than the comparison group. This pattern of increased reporting of medical conditions remained evident when the self-reports of medical conditions was restricted to those assessed by an HSA doctor as being ‘probable’ or ‘possible’ diagnoses, rather than being a ‘non-medical’ or ‘unlikely’ diagnosis.

This restriction was carried out in an attempt to improve the accuracy of the classification of subjects. There were some medical conditions that the Gulf War veterans reported as commonly as the comparison group. The physical medical conditions most commonly reported by Gulf War veterans were related to the musculoskeletal system, gastrointestinal system and skin. These have also been commonly reported in several overseas studies of Gulf War veterans.[16, 20, 21] Physical health status, as measured by the physical scale of the Short-Form-12 Health Survey (SF-12), was a little poorer in Gulf War veterans, but a greater difference was found for mental health status, consistent with the other findings in relation to psychological disorders.

The increased reporting of doctor diagnosed medical conditions, by Gulf War veterans compared with the comparison group, was much more focused on a few body systems, especially skin and gastrointestinal conditions, than the increased reporting of physical symptoms, which was much more widespread. This suggests that the increased physical morbidity in Gulf War veterans is at the less severe end of the health/disease spectrum for some, but not all, of the body systems, as they have not progressed as yet beyond symptoms to overt clinical disease and medical diagnosis. This interpretation is supported by the finding of increased recent functional impairment in Gulf War veterans, which does not necessarily require medical intervention, while no increase was seen in the current use of medications or increased hospitalisation, which do require medical input.

The physical health status of the Gulf War group was similar to that of the comparison group when assessed by objective clinical measures, as distinct from self-reported measures. This assessment encompassed a range of physical health measurements, such as blood pressure, body mass index, waist-to-hip ratio and a fitness step test. There was also no significant difference between the two groups in a wide range of laboratory investigations that were undertaken, including tests of the blood cells, function of the liver, function of the kidneys, biochemical indicators in the blood, measures of chronic inflammation and indicators of previous infections. While some of the Gulf War veterans' results were outside the expected range on many of these tests, a similar pattern was found in the comparison group. Two biochemical parameters, sodium and creatinine, were more commonly elevated in Gulf War veterans, but this difference was not thought to be clinically important at this stage. This suggests that there is no unique pattern of blood test abnormality in the Gulf War veteran group, for the blood tests investigated in our study.

This tendency for self-reported symptoms to be higher in the Gulf War group than in the comparison group, with little difference in objective measures of the same organ system, was found in particular for two organ systems examined in some detail in our study. These were the respiratory and neurological systems. For both of these organ systems, Gulf War veterans were more likely to report each of the respiratory or neuropathy symptoms than the comparison group. However, lung function measures showed little difference between the study groups. Neuropathic case definitions, based on combinations of symptoms and physical examination findings, identified a higher proportion of Gulf War veterans with these defined conditions, but a composite 'neuropathy impairment score' based on physical neurological signs only (from the HSA doctor's examination) showed no difference between the study groups.

Increased symptom reporting, found in conjunction with relatively normal objective measures of physical functioning, should not be interpreted as being of little importance in relation to physical health. Symptoms may indicate an early stage of disease, which is yet to manifest itself as clinical disease. Self perception of health and self-ratings of health have been shown

to be important predictors of future health care use and of mortality.[292, 354, 355] Leading indicators such as increased stress, poorer perception of health and premorbid indicators of ill-health may lead to more obvious health problems or increased mortality in the future. Whether or not these increased symptom reporting rates in Gulf War veterans will progress to clinical disease is something which cannot be answered by the present study. This could only be addressed in a follow-up study.

Of some concern to Gulf War veterans is the possibility that Gulf War service may have affected not only their own health, but also that of their offspring. Therefore, the investigation of reproductive outcomes was an important focus of our study. Although there were some problems with data quality (see below), the study does provide reassurance that adverse pregnancy outcomes, such as miscarriage, prematurity, low birth weight, malformations, or cancer in children were not more common in Gulf war veterans. While fertility problems in the post Gulf War period were a little more commonly reported in Gulf War veterans, they were more likely then comparison group subjects who reported such problems to subsequently father a pregnancy, so this reported reduction in fertility did not persist.

For some health outcomes there were too few cases on which to draw meaningful or definitive conclusions. An example of this is the finding of an increased risk of chronic fatigue syndrome in the Gulf War veterans. Only eleven cases of chronic fatigue syndrome were found in the Gulf War veteran group, while two cases of chronic fatigue syndrome were found in the comparison group. Despite these small numbers, the excess in the Gulf War group was statistically significant. However, factors which may have contributed to the increased risk of chronic fatigue syndrome could not be explored further. It is worth noting that Gulf War veterans more commonly reported, or were assessed as having, all other fatigue-related health outcomes that were considered in the process of defining cases of chronic fatigue syndrome, using a recognised set of published criteria for this condition. Applying these criteria does involve some judgement and it is possible that we applied these criteria too conservatively. However, as this was done blinded to the Gulf War status of the participants, these criteria were applied in a similar way in each group. Using a less conservative approach would give more cases of less severe fatigue conditions, which would increase the statistical power to be able to explore possible associated factors, albeit at the possible cost of reduced validity.

Most of the self-reported findings were based on standardised instruments, such as the CIDI and the SF-12, or questionnaires adapted from other Gulf War research groups, usually relying on closed questions where a response is ticked. Some measures to increase the accuracy of self-reported data were included, such as the assessment by an HSA doctor of self-reported medical conditions. These methods all helped to ensure high quality data as a basis for responding to the research questions. Unfortunately, there were other parts of the questionnaire where the data were collected using less standardised methods and which relied on the respondents to provide information in open data fields, resulting in poorer quality data. One example was the reproductive health data, in particular data in relation to birth defects and birth weight. Many of these fields were not completed in full by participants, or the quality of the data was too poor to be used. In addition, there was no verification of reproductive outcomes such as reported birth defects against either medical records or registries. For these reasons, the quality of the reproductive outcomes component of the study was poorer than the majority of other data collected in the study. Another example of doubtful data quality is in the documentation of immunisations. Those without the yellow immunisation books (about half of the Gulf War group) had very poor completeness of data

in relation to this potentially important exposure variable. Consequently, there is less confidence in the strength of the conclusions based on these variables.

In contrast, the mortality and cancer cohort study, which addressed two established population health indicators, did not rely on self-report, as we were able to utilise data from the national death and cancer registries to match against the names and other identifiers of the cohort. Both the National Death Index and the National Cancer Statistics Clearing House in Australia have good ascertainment of national deaths and cancer cases respectively. Therefore, the study design was very strong for this cohort study of mortality and cancer, with access to high quality data in the national registries. Our study found that the mortality and cancer rates of the cohort of Gulf War veterans and comparison group were considerably less than in the Australian community. The cohort is still quite young and the numbers of deaths and cancers are low at the present time. Therefore, prospective study of this cohort should provide more meaningful findings following future searches, as the cohort ages. This would also enable further exploration of the suggestive finding in the current analysis of an excess of disease-related deaths in the Gulf War cohort, compared with the comparison group. A factor which will be useful for future searches of the cohort, is that data on risk factors for cancer and mortality, such as tobacco smoking and alcohol intake, are available for those members of the cohort who took part in the cross-sectional study. This means that some adjustment could be made in the internal analyses for part of the cohort for these known confounders for tobacco and alcohol related cancers, following future matches.

The findings and conclusions discussed so far in this chapter relate to male Gulf War veterans. The health of female Gulf War veterans was considered separately from the male Gulf War veterans. This is because the number of female Gulf War veterans was considerably smaller than the male veterans and health patterns in males and females differ. Because of the small number of female Gulf War veterans, there was very low statistical power for almost all of the health outcomes investigated. Despite this, there was some degree of consistency with the results for the male Gulf War veterans, with female Gulf War veterans demonstrating some increased risk of psychological health outcomes, poorer self-perceived mental health status as measured by the SF-12 and GHQ and increased reporting of neuropathic symptoms. These findings, however, were not as strong or internally consistent as the findings for the men. Several of the most common symptoms reported by female Gulf War veterans were also the most common symptoms reported by male Gulf War veterans. Female Gulf War veterans, however, only reported about half of the general health symptoms more commonly than the female comparison group, suggesting that the differences in general health indicators were not as marked as for the male Gulf War veterans.

The other major area of the study, which generated interesting findings, was the assessment of exposure and experiences, in particular during the Gulf War itself, but also during other deployments. After analysing these data it became clear that there were several major experiences and exposures which appear to be almost unique to the Gulf War. These were taking NAPS tablets, exposure to SMOIL, fear of exposure to depleted uranium, the threat of chemical or biological warfare and the consequent use of protective clothing and equipment. Most Gulf War chemical and environmental exposures were reported at similar rates to those reported by veterans from overseas studies. A consistent theme evident in the Military Service Experience questionnaire was the high reporting of fear or threat of an enemy attack, death or injury, rather than the actual experiencing of these things. These were more commonly reported during the Gulf War than during other military service activities, including other active deployments. The findings were quite similar between male and female Gulf War veterans. As was the case with the male veterans, a high proportion of

female veterans reported experiencing fear of death or injury and the threat of a chemical warfare attack during the Gulf War.

This may be an important factor in why Australian Gulf War veterans appear to be at greater risk of a wide range of psychological disorders and physical symptom reporting, and to a lesser extent other physical health problems, than other ADF personnel serving at the time of the Gulf War. The Gulf War was a very short war, Australia played mainly a support role with little involvement in direct battle, and there were no Australian deaths and few casualties. What is suggested from the results of our study, is that it was not the actual combat experience during the ground war and air war, which has had the biggest impact on Australians deployed to the Gulf. We found no consistent or major differences in the patterns of health outcomes between veterans who had completed their deployment before the air strikes and ground war commenced and those who did not.

What seems to be more important, from the responses to the military experiences questionnaire, was a consistent theme of fear of enemy attack including threat of possible chemical or biological attack. Unlike conventional weapons, chemical and biological weapons can be used against people without it being readily or immediately apparent. This was compounded by many false alarms including frequent sounding of chemical alarms, requiring the unnecessary use of protective suits and preventive medications. It can be hypothesised that this prolonged sense of uncertainty about whether unseen, but deadly, weapons may strike or had struck could be a major source of personal fear in Gulf War veterans. This could therefore have been one of the more important reasons for the later development of psychological disorders and an increased awareness of physical symptoms. This continued uncertainty about whether such possible attacks by chemical weapons had in fact occurred during the Gulf War is likely to have continued after the Gulf War, particularly as there was considerable publicity about this in the scientific literature, media and in the veteran community itself.

One last point to note is that, apart from the scientific benefits of conducting this study, it appears likely that the overall experience of participating in the study was a positive one for those veterans involved. As well as being asked a series of standardised questions, the Gulf War veterans were provided with the opportunity to relay personally important, additional health and exposure information in open text fields in the postal questionnaire. They also had the chance to discuss health concerns with an HSA doctor during the health assessment, which many found beneficial. Further, all participants received a written summary of their health findings. Despite concern that raising issues about possible stressful events during the Gulf War may cause distress to participating Gulf War veterans, there was no evidence that this was common and, if this did occur, procedures were in place to minimise any distress. No known complaints were made to any of the Ethics Committees which had approved the study and where feedback was provided to the study team from participants, this was invariably positive.

19.4 Strengths and limitations of the study

The study had many strengths, especially when considered in relation to overseas studies of the health of Gulf War veterans. Firstly, it was decided to include all of the Gulf War veterans in the study and attempts were made to contact all 1873 Gulf War veterans on the Gulf War Nominal Roll. This meant no potential sampling error was introduced for the Gulf War veteran group.

Secondly, the study included a well-matched comparison group. This group was drawn from the ADF personnel classified as 'operational' or 'fit to deploy' at the time of the Gulf War, as were the Gulf War veterans. This reduces the likelihood of pre-existing differences in health status between the two groups, as members of each group would have had to have reached a certain degree of medical fitness to be classified as operational. Secondly, matching on the basis of age, service type and rank reduced the potential for differences in health outcomes to be explained by these confounding variables. Although not specifically matched on this basis, the groups also had similar rates of important lifestyle factors, such as tobacco smoking and alcohol intake. This similarity in lifestyle factors, and subsequent adjustment for them in the analyses, meant that these factors were unlikely to explain differences in health between the two groups.

A third strength of the study was that we collected a large amount of information on exposures, to allow us to explore the relationship between specific aspects of Gulf War service and health outcomes. This has been less thoroughly investigated in much of the overseas Gulf War veteran research. Although much of the exposure assessment relied on self-report of data, there were some more objective measures of exposure which were used to develop exposure metrics, such as completion of deployment prior to the commencement of the air war. In addition, all participants were asked about a range of other exposures and experiences during their military and civilian careers, including those related to their other deployments. There were no major differences between the two study groups in these exposures, which suggests that exposures and experiences unrelated to the Gulf War are unlikely to explain large differences in adverse health effects between the two groups.

Fourthly, we included several objective tests of health indices, rather than relying solely on self reports from the participants themselves. Many overseas studies had relied almost entirely on self-reported health data, which weakens the study design in those studies. Even where we used such self-report data, we were sometimes able to review it with the participant to ensure its accuracy. For example, the HSA doctors further questioned the participants on their self-report of doctor-diagnosed medical conditions, and were able to apply a confidence rating to such diagnoses.

A further strength for such a large multidimensional study was having a large group of senior investigators with diverse expertise in a wide range of health research areas, as well as additional collaborators in those areas where the investigators felt the study needed further specific skills and knowledge. In addition, the study was undertaken in a strong research environment by a research team, which remained together over the almost three year duration of the study. This was complemented by the extensive network of HSA clinics throughout the country, which facilitated consistent data collection procedures. Good communication links were established between the Monash study team, HSA management and the HSA clinics and staff throughout Australia, and the DVA Contact and Recruitment team. This involved over 100 people and it was important to ensure all individuals and groups understood the objectives and their individual role and to put in place good communication and monitoring systems.

Several procedures were instituted to make contact with potential participants and to maximise participation. These included the development of a tracking database which was used to follow participants and their data through the entire sampling, recruitment, assessment and data entry phases of the study. Appointments for the health assessment at HSA were offered at various offices around the country, the time of the appointments were flexible, evening and Saturday appointments were offered. Participants were offered

reimbursement of travel costs and for lost earnings. In addition we undertook extensive checking of the data and direct phone follow-up with participants to ensure as high as possible data quality and completeness.

The establishment of the Consultative Forum, with representatives from a wide range of veteran and service groups, was another strength of the study. This forum played a key role in communicating the aims of the study among veteran and service networks and also provided the study team with important information from the veteran and service communities. This assisted in the development of the content of questionnaires and other data forms, and in addressing privacy and confidentiality issues. In addition, the Scientific Advisory Committee for the study was an important forum for discussion of the study design and analytical approaches.

There were, however, some limitations to the study. Firstly, it needs to be pointed out that this was a cross-sectional survey undertaken at one point in time more than ten years after the Gulf War. Therefore, it is difficult to attribute with absolute certainty any excess in health problems specifically to this part of the veterans' lives, especially as no pre-existing health data from prior to the Gulf War were able to be accessed for comparison purposes. This can be done with more certainty where information on the health of participants is collected at different stages over time, such as in a prospective cohort study. Nevertheless, the inclusion of a comparison group drawn from the ranks of the ADF at the same time as the Gulf War veterans does help to give more weight to the conclusions.

Participation bias was a potential problem, not so much for the Gulf War group where the participation rate was over 80%, but for the comparison group where the participation rate was only about 57%. The research team had anticipated, based on the experience in overseas studies, that participation by the comparison group was likely to be considerably lower than that of the Gulf War group. Therefore, some health and lifestyle information was sought from non-participants in a telephone questionnaire, to enable us to assess the degree of participation bias and the impact this could have on our interpretation of the study findings. The possible effect of participation bias was modelled for several, but not all, of the important health outcomes. There are limitations to the interpretation of the participation bias analysis, which was based on information drawn from the telephone questionnaire responses, and on predictions of health outcomes in non-participants derived from patterns observed in participants. However, the results suggest that any effects of participation bias are likely to be small and unlikely to explain the larger health differences between the study groups, such as those for psychological disorders.

One factor which has been raised as a possible reason for increased symptom reporting in Gulf War veterans is recall bias, which means that if veterans are concerned by their Gulf War service, they are more likely to focus on symptoms which may also be common in everyday life. However, while we found that all symptoms were consistently higher in the Gulf War group, other self-reports, such as for medical conditions or exposures, did not show the same pattern of all being reported in excess. In addition, Gulf War veterans and comparison group participants were almost equally as likely to have their self reported medical conditions assessed as 'possible or probable' by a HSA doctor, suggesting that recall bias was not occurring in relation to this self-reported health measure. Therefore, there is not strong evidence to suggest the increased symptom reporting can be explained entirely by recall bias.

Another factor which limits interpretation of the effect of Gulf War exposures, is that much of the exposure information was reported by the veterans themselves. This relied on their

memory of events many years in the past, which may not always be accurate. This was compounded by the fact that only for some exposure variables was objective information available to validate self-reported exposure information. A good example of the possible impact of this was the difference in findings in relation to DU exposure and being in an area where chemical warfare agents had been used. For DU exposure, we combined self-report with other information on possible exposure to DU during the Gulf War to develop the DU exposure metric. In contrast to this, we relied only on self-report for developing the exposure metric for being in an area where chemical warfare agents had been used. In the analysis, we did not find that DU was associated with any health outcomes, whereas being in an area where chemical warfare agents had been used was associated with several health outcomes. People with health problems may be more likely to remember exposures, leading to a form of information bias, and this could be a possible explanation for the difference in findings for DU and being in an area where chemical warfare agents had been used.

Another aetiological problem in relation to exposures is that many veterans were co-exposed to vaccinations, NAPS tablets, stressful experiences and perhaps several chemical and environmental exposures such as sunscreen, solvents and fuel. Those veterans who reported believing that they had been in an area where chemical warfare agents had been used were consequently also likely to have been co-exposed to the uncomfortable use of respiratory protective equipment and protective clothing. When so many co-exposures are present, it can be difficult to identify with certainty which exposure may be the most important one in terms of causation. This was the case with several of the general health outcomes, where associations were found for many exposures and experiences in the Gulf, rather than just one of these exposures.

Confounding factors or effect modifiers also need to be considered as possible explanations for the findings in this study. When the male Gulf War veterans were compared to the comparison group on a range of factors such as service type, rank, education level, socioeconomic status, smoking rates and alcohol intake, the groups were very similar. The Gulf War group was a little older than the comparison group, as younger people in the comparison group were a little less likely to take part. All analyses were adjusted for a core set of these possible confounders to ensure they were not the explanation for any differences in health status found between the two groups. In addition, possible confounders relevant to the particular health outcome under consideration, such as alcohol intake or a history of diabetes in relation to neurological health outcomes, were also considered. Also, Gulf War veterans and the comparison group were similar in respect of the exposures and experiences reported on active deployments other than the Gulf War, in the rest of their military history and during their civilian careers. However, there is always the possibility of other confounders, which have not been considered.

Another potential problem was that there were many hundreds of analyses undertaken during the data analysis phase of our study. Applying a statistical significance level of 0.05, as we have done, with such a large number of statistical analyses, means that we could find associations between exposure and adverse health outcome on the basis of chance alone. This can lead to Type I errors, where false associations are found, leading to erroneous conclusions. To overcome this problem in epidemiological research generally, corrections to the level of statistical significance have been proposed, such as the Bonferroni correction.[422] Other authors have argued that such corrections are unnecessary.[423] This is not the place for a detailed discussion of the pros and cons of such an approach, but we decided for this study not to apply a statistical correction. Instead, we have decided to approach the potential problem of multiple comparisons in a less statistical way. While we have considered 95%

confidence intervals in drawing our conclusions from the study, we have tended to give more weight to those findings where consistent patterns have been shown in several different analyses, where these confirm similar findings in overseas studies or where there is a biologically plausible reason for the findings. For those readers who believe that a statistical correction to the level of significance assists in their interpretation of the data, we have included P values in the tables in the results chapters, to enable a Bonferroni or other correction to be carried out.

In summary, the study design for the Australian Gulf War Veterans' Health Study had several strengths over many previous studies of Gulf War veterans, which has allowed us to investigate more health outcomes, and to better assess the possible effects of Gulf War experiences and exposures. There are inevitable limitations in this type of study, but we were able to anticipate many of these and build into the study design and analysis several measures to reduce the impact of these factors. Nevertheless, factors such as participation bias and recall bias cannot be completely excluded as at least partly explaining some of the findings.

19.5 Further research

While the findings presented in this report have been able to address, either fully or partly, the research questions developed for the study, the analysis so far has highlighted several other important areas where further analysis of the existing dataset could improve our understanding of the relationship between Gulf War Service and health:

- While we have established that the number of adverse experiences in the Gulf War is associated with several of the psychological disorders, it is not entirely clear which of these experiences are playing a more important role. Further analysis of the Military Service Experience questionnaire could establish which particular types of stressful experiences during Gulf War service are more highly associated with psychological disorders than others. This could also involve validation of the Military Service Experience Questionnaire, to enable it to be used in future studies of deployed ADF personnel or in intervention studies to establish the success of different training methods in anticipation of stressful experiences, or subsequent debriefing methods, in preventing longer term psychological health problems.
- While we have demonstrated that the number of immunisations is related to several of the physical health outcomes, this conclusion is tempered by the fact that many of the Gulf War veterans were not able to refer to their immunisation books or other records. To better explore the relationship between health outcomes and immunisations, it would be useful to do consistency checks between people on the one ship in relation to immunisation reports for those who had an immunisation book and those who didn't. As part of this, it would be useful to undertake verification of a sample of the immunisation reports by comparison to the WHO immunisation books, for those who had them.
- Some blood and serum samples have been collected during the study and put into short and long term storage. These could be used to investigate other health outcomes which may be important in the health of Gulf War veterans, but were not part of the original Australian Gulf War Veterans' Health Study research questions. This would require further approvals by the relevant Ethics Committees. For example, a proposal has been received by the study team from researchers interested in the investigation of genetic polymorphisms in relation to PTSD. Another possibility is to investigate Mycoplasma serology, as this infection has been suggested as a possible cause of illness in Gulf War veterans, but this is yet to be published in the scientific literature.

- There were insufficient numbers of chronic fatigue syndrome to evaluate Gulf War factors, which may have contributed to the excess risk of this condition found in Gulf War veterans. Investigation of chronic fatigue, based on less rigorous criteria than those required to define chronic fatigue syndrome, would give more cases and would allow further investigation of Gulf War exposures, albeit with possible reduced validity.
- While we found that there was no difference between the groups on respiratory function, this is tempered by the fact that many of the participants weren't able to complete the lung function testing to ATS standards. Further analysis of the respiratory data could include identification of the characteristics of these participants. A higher proportion of Gulf War veterans was unable to perform health spirometry to this standard and it is possible that this is a result of underlying respiratory disease.
- Exploration of the relationship between physical and psychological disorders in Gulf War veterans was not specifically part of the research questions. As both psychological and physical health outcomes have been found in excess in this group, there may be some important inter-relationships which could be explored within the existing dataset.

As well as further analyses of the existing dataset, there are several possible avenues for follow-up studies of the whole group or particular subgroups, where further data would need to be collected. Such studies are important to undertake where the data collected in the current study were not able to fully answer a particular research question, where the current study was at too early a stage to be able to explore a particular health outcome adequately or where further important research questions have been raised by the findings in the current study. These studies could also be undertaken in response to future published findings in overseas studies, which are of relevance to Australian Gulf War veterans. Examples of these include:

- Follow up matching studies of the NDI and NCSCH will be needed to investigate cancer types and causes of death, as the numbers are currently too small to be able to investigate these in a meaningful way. The two cohorts should be maintained for this purpose, live status ascertained and the NDI and NCSCH data accessed every few years to establish the ongoing mortality and cancer rates of the Gulf War veterans and their comparison group.
- Neurological symptoms suggestive of peripheral neuropathy were found to be more common in Gulf War veterans. To investigate this further, a follow up case control study would need to be conducted to undertake nerve conduction studies of defined cases and selected controls.
- There is also the opportunity to follow some subgroups of the Gulf War veterans who have been found to have specific disorders, such as PTSD, to document longer term sequelae of these health outcomes and to assess possible interventions.
- The health status of all members of the two groups could be followed into the future. Increased symptom reporting, increased medical condition reporting and poorer perception and self-ratings of health may be early indicators of more serious health outcomes occurring in the future. Increased psychological health abnormalities have also been shown to lead on to later physical health problems. The only way to assess whether this will occur in the future will be to undertake a follow-up health study, to enable comparisons to be made with the baseline data collected as part of the current study.

The third major area of possible research relates to further investigation of those health outcomes which were found to be high in both groups, not just in the Gulf War group. These include high body mass index and substance use disorders. The study has collected a large amount of data which relate to military service in general and other non-Gulf War deployments. The dataset includes information about the health of Gulf War veterans and the

comparison group but also includes information about exposures and experiences during these other deployments and the rest of their military and civilian careers. Therefore, it would be possible to use this dataset to undertake analyses to investigate the effect of other aspects of service on health.

In conclusion, the dataset and the subjects in the two groups who have taken part in the study should be seen as a unique resource, which could be used to investigate health patterns in ADF personnel, including veterans of other deployments. This would be beyond the scope of the research questions for the present study as they would not just relate to Gulf War service. More detailed analyses of the current dataset or follow-up of participants in the current study would increase our understanding of health patterns and risk factors in ADF personnel, which could be used to assist in the identification of preventive health measures for these personnel.

19.6 Recommendations

While the main focus of this report has been to document the study findings in relation to the health of Gulf War veterans, we have also formulated a few key recommendations in relation to communication of the study findings, application of the findings, possible avenues for further research and measures to make such studies easier to undertake in the future. These recommendations, with some explanatory notes, are:

1. **There should be wide promotion of the study findings to the veteran and service communities, the Departments of Defence and Veterans' Affairs, the Repatriation Commission, ADF Medical Officers, the broader Australian community and the scientific community.**
   The findings of this study are likely to be important factors in diagnosis and management of Gulf War veterans and in consideration of entitlements for these veterans.

2. **Consideration should be given to measures to reduce adverse psychological impacts of military service or deployment related activities on Defence Force personnel, especially in relation to better psychological preparation for the possibility of chemical or biological weapons attack**.
   Such weapons are likely to remain a threat in future conflicts. Having a deployed or deployable force which is psychologically better prepared, as well as more reliable systems for monitoring whether biological or chemical attack have in fact occurred, may assist in reducing the fear associated with the threat of such attack and subsequent psychological morbidity.

3. **Consideration should be given to developing a minimum health dataset collected routinely in a standardised manner on all individuals before active deployments**.
   Health status information for Gulf War veterans, which predated the Gulf War or was collected routinely at the time of deployment, would have provided extremely useful baseline data against which the health of veterans could later be compared.

4. **Consideration should be given to developing procedures for more accurately documenting exposures during active deployments**.
   One of the difficulties for our study was the paucity of accessible, well documented exposure data from the time of the Gulf War. This includes information on immunisations and preventive medications, such as pyridostigmine bromide.

5. **Consideration should be given to the further development, including validation, of the Military Service Experience questionnaire for use in practice to assess the effect of deployments and in future studies.**

This questionnaire could become a standard measure of deployment-related stressors for ADF personnel, to be used as a predictor for psychological health outcomes and in any future psychological health intervention studies.

6. **Consideration should be given to undertaking further analyses of the dataset and/or collecting further data to address other questions raised about the impact of Gulf War service, or other aspects of military service, on health.**
The data collected during this study is a unique resource, which could be further analysed to answer further questions in relation to the effects of Gulf War service, other deployments and other aspects of military service on health outcomes, especially where there were problems of small numbers or poor data quality. Examples are immunisations and chronic fatigue. This could be supplemented by further data collection for some health outcomes, such as peripheral neuropathy, which the study was not able to adequately address.

7. **Consideration should be given to undertaking follow-up studies, especially in relation to the cohort mortality and cancer study, but also in relation to some of the health outcomes found in excess in Gulf War veterans, such as posttraumatic stress disorder.**
The mortality and cancer study will only start to provide useful data to investigate causes of death and different types of cancer as the cohort ages. Follow-up studies for other health outcomes, such as posttraumatic stress disorder, skin disorders and symptom reporting, found in excess in Gulf War veterans, will document the longer term outcome of these effects.

8. **A Board of Trustees should be appointed by the Repatriation Commission for the purpose of governing future access to the serum held in long-term storage.**
The Board of Trustees should consist of members representing Monash University, the Department of Veterans' Affairs and the veteran community.