Presentation 10 – Beatrice Golomb

Update on Research in Persian Gulf War Veterans Illnesses May 2006

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Epidemiology

- UK: "Operation Granby": no special syndrome
- Kang Group: Chronic multisymptom illness 10 years later
- UK: Mortality by deployment experiences
- Khamisiyah Model and Outcomes

Op Granby Study

- Conclusion: "There is nothing …in this analysis to support the media publicised suggestion of a specific Gulf War Syndrome or any unique Gulf service related illness" "We found no evidence of a unique "Gulf War Syndrome." "All illnesses are accounted for by well-established ICD-10 classifications. We have not found any medically unexplained conditions."
- Subjects: 3233 Gulf Veterans who attended Op Granby (UK) medical assessment program. Mean age 34 (58% under this age)
- Methods: "Over a period of 10 years, 3233 veterans have been assessed" with "in-depth interviews, full medical examination and appropriate investigation." "All diagnoses have been made according to ICD-10 classifications. All psychiatric diagnoses have been confirmed by consultant psychiatrists"

Bale 2005. J Royal Naval Medical Service 91: 99-111.

Op Granby Study

Outcome: The categories used were

1. Well completely (asymptomatic)

2. Well with symptoms but "no disease"

3. Well with incidental diagnoses:

- **Only psychiatric**
- **Only organic**
- **Both**

4. Unwell:

- **Only psychiatric**
- **Only organic**
- **Both**

Bale 2005. J Royal Naval Medical Service 91: 99-111.

Op Granby Study

Findings:

- "75% of veterans were well"
- Of the 25% unwell, 83% of ill health was "accounted for" by a psychiatric disorder.
- "The most commonly seen disorders amongst veterans here were of a psychiatric nature, confirming our previous findings. The most frequently seen condition was PTSD 12% with or without comorbidity and 93% were Gulf Service related".
- "3% of veterans had an organic conditions that could be linked to Gulf deployment. The most common were respiratory, digestive, and skin disorders. Only 11 of these cases could be linked to the use of medical countermeasures."

Bale 2005. J Royal Naval Medical Service 91: 99-111.

Op Granby Study

Alternative Analysis: The categories used were:

1. Well completely (asymptomatic): 10%
2. Well with symptoms but "no disease": 27%
3. Well with incidental diagnoses: 39%
   - Only psychiatric: 7%
   - Only organic: 29%
   - Both: 3%
4. Unwell: 25%
   - Only psychiatric: 14%
   - Only organic: 4%
   - Both: 6%

Thus: 27% + 29% + 3% + 4% + 6% (69%) have symptoms or organic diagnoses; excluding concurrent psych: 60%

Bale 2005. J Royal Naval Medical Service 91: 99-111.

Op Granby Study

Limitations:

- No epidemiological assessment of relation of exposures to symptoms OR to conditions: but concludes that most conditions not be linked to exposures or countermeasures. Appears to assume its conclusion.
- Presumes attachment of an ICD-10 code implies an "explanation" – thus no "medically unexplained conditions"
- No control group against which to assess rates
- [codes include things like: shoulder pain; toxic myopathy]
- Cites in discussion negative findings (no overall increase mortality or cancer); fails to cite or dismisses findings suggestive of health problems (e.g. immune findings shown to differ in GWV)

Bale 2005. J Royal Naval Medical Service 91: 99-111.

Op Granby Study: Discussion

"Many veterans came here with known diagnoses but wanted reassurance that their problems were not related to service in the Gulf. Having been given such reassurances, these veterans went away satisfied as per data gathered from anonymised patient satisfaction questionnaires" [data not shown]

"Some studies have suggested neurological disorders and parasympathetic autonomic nervous system dysfunction as a result of Gulf service but such studies have been poorly controlled and numbers recruited extremely small" [They did not do parasympathetic measures; or have a control group, so no basis for comment]

"There have been media claims of disorders of the immune system…. Elsewhere no evidence of abnormal immunological responses in Gulf War veterans has been found (Everson 2002). Another study suggested there might be altered immune cellular activation in Gulf veterans. Their results were debatable given they were 9 years after service in the Gulf." [Comment: there is a control group; and they have no basis to refute: they did not present immune measures or have a control group]

Bale 2005. J Royal Naval Medical Service 91: 99-111.

Chronic Multisymptom Illness Complex (CMI) in GWV 10 Years Later

Finding: Chronic medical illness (CMI) continues to be substantially more prevalent among deployed veterans than among nondeployed veterans 10 years after the War, but it manifests similarly in both groups

Blanchard MS 2006 Chronic Multisymptom Illness Complex in Gulf War I Veterans 10 years Later. Am J Epi 163: 66-75

CMI in GWV 10 Years Later

Subjects: National Health Survey of Gulf War Era Veterans and their Families in 1995-6. From Kang et al stratified random sample surveys sent to 15K deployed and 15K nondeployed veterans among cohort of 693K Gulf deployed and 800K nondeployed era personnel.

- 11441 deployed, 9476 era participated.

Outcome:CMI: Modified Fukuda CDC definition, >6mo of sx from 2/3 categories of fatigue, mood/cognition, "musculoskeletal pain". But used responses to spec sx questions to define this. E.g. unusual fatigue following exertion that lasts for at least 24 hours' or "feeling depressed"

-- To be "severe" at least 1 sx in each case defining cluster had to be severe.

Factors that analysis assessed in relation to CMI:

- QOL: SF-36
- Medical History: "Have you ever been told by a physician that you have"
- Medical Conditions: HTN (conservative, BP >160/100 or hxHTN+(Meds or BP>140/90), leukopenia <3.5Kcells/mm3, renal insuffic >1.5 creat, leukocytosis >11K, waist:hip ratio cutoff not given, Metabolic syndrome by NCEP: glc>110, waist >40men 35 women, TG>150, HDL<40, and HTN
- Psychiatric d/o by CIDI structured interview

Problem: picked med conditions to be those with prewar assoc to CMI (p >.25); expect these also related in any popn then.

Blanchard MS 2006 Chronic Multisymptom Illness Complex in Gulf War I Veterans 10 years Later. Am J Epi 163: 66-75

CMI in GWV 10 Years Later: More CMI; especially more severe CMI

CMI:	Deployed n=1035	Nondeployed n=1116	OR	95% CI
All cases	327 (28.9%)	165 (15.8%)	2.2	1.6-2.9
Mild-mod	257 (24.8%)	142 (14.7%)	1.9	1.4-2.6
Severe	70 (7.0)	23 (1.6)	4.7	2.3-9.5

Blanchard MS 2006 Chronic Multisymptom Illness Complex in Gulf War I Veterans 10 years Later. Am J Epi 163: 66-75

CMI 10 yrs later: CMI are sicker

	Deployed				Nondeployed			
	CMI	**Not**	OR	P-or-CI	**CMI**	**Not**	OR	P-or-CI
	n=327	*n=708*			*n=165*	*n=951*		
PCS	**43**	**53**		**<0.001**	**44**	**52**		**<0.001**
MCS	**43**	**51**		**<0.001**	**46**	**54**		**<0.001**
≥1 nonroutine clinic visit in last yr	**71**	**52**	**2.3**	**1.4-3.5**	**74**	**54**	**2.4**	**1.5-3.9**
≥1 hospitalization in last yr	**5.1**	**3.3**	**1.6**	**0.63-4.0**	**9.6**	**4.5**	**2.3**	**1.02-5.1**
Mean # prescripx meds	**1.2**	**0.57**		**0.002**	**1.3**	**0.81**		**0.004**
≥1 psychotropic meds	**10**	**3.0**	**3.8**	**1.7-8.2**	**17**	**3.7**	**5.5**	**2.8-10.7**

Blanchard MS 2006 Chronic Multisymptom Illness Complex in Gulf War I Veterans 10 years Later. Am J Epi 163: 66-75

CMI: Relation to Medical Conditions

CMI linked to:	Deployed			Nondeployed		
	%CMI vs %non	OR	CI	%CMI vs %non	OR	CI
- Fibromyalgia	5.2 >0.7	7.4	2-27	3>0.8	3.9	1.2-13
- CFS	5.7>0	∞	n/a	0.6>0.0	∞	n/a
- Dyspepsia	16>6	3.2	1.6-6.1	12>4.8	2.6	1.3-5.4
- Arthralgias	9.8>3.5	3.0	1.4-6.7	13.4>5.4	2.7	1.4-5.2
- Metabolic synd	25>13	2.2	1.3-3.7	30>19	1.9	1.2-3.1
- HTN	14>9	1.6	0.9-2.9	20>14	1.4	0.8-2.5
- ObstruxLungDs	4.4=4.5	.99	.4-2.5	7.8>5.6	1.4	0.7-3.1
- DM	3.7<4.5	0.8	0.3-2.3	5.2>3.0	1.8	0.6-5.0
- Waist:hip, men	.93>.91	p = 0.004		0.95>0.92		p = 0.001

BUT conditions examined=those w/prewar reln to CMI w/ p <0.25 (&prevalence>.2)

Blanchard MS 2006 Chronic Multisymptom Illness Complex in Gulf War I Veterans 10 years Later. Am J Epi 163: 66-75

Chronic Multisymptom illness Complex in Gulf War I Veterans 10 Years Later

CMI link to:	Deployed			Nondeployed		
	%CMI>non	OR	CI	%CMI>non	OR	CI
PTSD	6.1>2.0	3.2	1.2-8.7	7.5>1.1	7.1	2.3-22
Major depression	16>4.2	4.4	2.3-8.8	14>3.1	5.3	2.6-11
Anxiety disorder	22>6.1	4.3	2.4-7.8	22>5.5	4.8	2.7-8.7
1 or more mental d/o	39>12.7	4.4	2.7-6.9	38>11	5.1	3.1-8.3
Alcohol dependence	3.3>0.7	4.8	1.1-21	0.5>0.4	1.3	.22-7.4
Nicotine dependence	19>8.1	2.6	1.4-4.8	16>5.6	3.3	1.7-6.3

Blanchard MS 2006 Chronic Multisymptom Illness Complex in Gulf War I Veterans 10 years Later. Am J Epi 163: 66-75

Chronic Multisymptom illness Complex in Gulf War I Veterans 10 Years Later

Conclusion:

- CMI occurs in deployed and nondeployed
- It is more common in deployed, especially severe form
- "Similar relations to physical and mental illness in both groups"

However: differences as well as similarities may be worthy of note:

- GW -> More symptom based diagnoses focused on fatigue and muscle
- Nondeployed -> More Diagnoses "expected" to produced sx

Limitation: Included only conditions assoc with CMI prewar. Since GW should not protect against CMI induced by these, expect also related postwar. Didn't look for conditions only related postwar; further limits conclusion of similar relations to phys illness in these groups.

Blanchard MS 2006 Chronic Multisymptom Illness Complex in Gulf War I Veterans 10 years Later. Am J Epi 163: 66-75

Mortality as a Function of Deployment experiences in UK GWV

Finding:

Overall no difference in death rate in UK GWV vs Era controls*.

Within GWV: Association of exposure to mortality strongest for handling DU, anthrax, and handling pesticide (& scud missile passed nearby). Pattern of deaths differs:

Pesticides, anthrax, scud -> nondisease deaths;

DU, anthrax (and pertussis) -> disease deaths

PB, CW not included

*Recall sick people not selected for deployment; "healthy warrior"

Macfarlane, Hotopf et al 2005. Long term mortality among Gulf War veterans: is there a relationship with experiences during deployment and subsequent mortality? Int J Epidem advance copy pub Oct 26, 2005

Mortality vs Exposures: UK GWV

Subjects: 51,753 UK GWV; 50,808 Era. GWV in-Gulf btn 9-90 and 6-91 vs random sample of nondeployed era personnel "group-matched" for age-band, sex, service branch, rank, fitness for active service(for army and RAF). Recall prior Unwin study. #s given are after losses/exclusions: initially 53,462 each group.

Exposures examined:

- Vaccinations (pertussis; plague; anthrax; "all" (all 3 of these))
- Handled pesticides. Living quarters sprayed with pesticides. Personal pesticide or insecticide use.
- DU
- Smoke from oil fires
- Scud missile passed nearby
- Came under small arms fire
- (Not PB; CW)

Outcomes: death; disease death; nondisease death

Analysis: Mortality Risk Ratio by Cox proportional hazards

Adjustment: age-group, gender, service (regular/reservist), branch (army, Navy, RAF), smoking, alcohol consumption Macfarlane, Hotopf et al 2005. Int J Epidem advance copy Oct 26, 2005

Mortality vs Exposure: UK GWV

	Disease Deaths		**NonDisease Deaths**	
Exposure	Adj MRR	95% CI	Adj MRR	95% CI
DU	**1.99**	**0.98-4.0**	0.78	0.2-2.5
Anthrax vaccine	**1.34**	**0.8-2.2**	1.16	0.6-2.2
Pertussis	1.15	0.7-1.8	0.85	0.4-1.6
Scud passed nearby	0.98	0.6-1.6	**1.38**	**0.7-2.6**
Smoke from oil fires	0.96	0.6-1.5	0.65	0.4-1.2
Personal pesticides	0.87	0.5-1.4	0.95	0.5-1.7
Handled pesticides	0.85	0.3-2.1	**2.05**	**0.9-4.6**
Pest sprayed quarters	0.78	0.4-1.4	**1.31**	**0.7-2.5**
Plague	0.82	0.5-1.3	1.01	0.6-1.8
Came under small arms fire		0.89	0.4-1.9	0.46 0.2-1.3
PB, CW	**Not assessed**			

Adjustment: age-group, gender, service (regular/reservist), branch (army, Navy, RAF), smoking, alcohol consumption. Self reported exposure to DU: ? How asked

Macfarlane, Hotopf et al 2005. Long term mortality among Gulf War veterans: is there a relationship with experiences during deployment and subsequent mortality? Int J Epidem advance copy pub Oct 26, 2005

Mortality vs Exposures: UK GWV

	% Exposed	Adj MRR	95% CI
DU	**7**	**1.48**	**0.8-2.6**
Anthrax vaccine	**72**	**1.21**	**0.8-1.8**
Handled pesticides	7	1.19	0.7-2.2
Scud passed nearby	24	1.15	0.8-1.7
Pertussis	33	1.05	0.7-1.5
Pest sprayd Living quarters		22	1.030.7-1.6
Personal pesticides	53	0.91	0.6-1.3
Plague	45	0.90	0.6-1.3
All vaccines	25	0.88	0.6-1.3
Smoke from oil fires	65	0.83	0.6-1.2
Came under small arms fire		18	0.620.3-1.2
PB, CW	**Not assessed**		

Attributable risk 3% DU (.07*.48), 15% AxVax (.72*.21), if MRR upheld

Macfarlane, Hotopf et al 2005. J Epidem advance copy Oct 26, 2005

Do Symptoms Relate to Death?

Symptom Tertiles	Adj MRR	95% CI
All Deaths		
Lowest	**1**	
Middle	**0.51**	**0.2-1.4**
Highest	**1.17**	**0.6-2.4**
Disease Deaths (will require ongoing eval for 40% incr to be signif – if sustained)		
Lowest	**1**	
Middle	**0.3**	**0.06-1.4**
Highest	**1.4**	**0.6-3.4**
NonDisease Deaths		
Lowest	***1***	
Middle	***0.93***	***0.2-3.7***
Highest	***0.88***	***0.3-3.1***

Comment: Symptom Nonreporters Do Worse than Those Citing Middle Symptoms. Very ill may not put self at risk (My GWV is getting pilot lessons; healthy people die of accidents)

Macfarlane, Hotopf et al 2005. Long term mortality among Gulf War veterans: is there a relationship with experiences during deployment and subsequent mortality? Int J Epidem advance copy pub Oct 26, 2005

Mortality Relations

Conclusions:

Some exposures may be linked to increased mortality

- Need to Look at PB (and CW?)
- Adjust for other exposures?

High sx reporting may be linked to mortality; need larger N

Low sx reporting may be linked to mortality (reporting vs hyporesponsive)

Macfarlane, Hotopf et al 2005. Long term mortality among Gulf War veterans: is there a relationship with experiences during deployment and subsequent mortality? Int J Epidem advance copy pub Oct 26, 2005

"Khamisiyah" Outcomes

2 studies:

I. Little association between potential exposure (2000 plume model) to sarin or cyclosarin and self-perceived health status after adjusting for covariates.

II. Comparing notified to nonnotified subjects, there were no significant differences in bed days, activity limitations, clinic visits, or hospital visits. 5 among 71 self-reported medical conditions and symptoms were significantly different – 4 of which were lower in notified subjects.

Mahan, Page, Bullman, Kang 2005. Part I. Morbidity Associated with Potential Exposure. Military Medicine 170: 935-944.

Page, Mahan, Kang, Bullman 2005. Part II. Morbidity Associated with Notification of Potential Exposure. Military Medicine 170:945-951

"Khamisiyah" Outcomes

Subjects: From Kang stratified sample of "15,000" each Gulf and NonGulf, use subsample of 1200 respondents to the National Halth Survey intended to have equal numbers exposed and nonexposed Army veterans; and notified and nonnotified Army subjects. "but inadvertent inclusion of nonarmy subjects meant final sample only 1056, of whom 72% (756) responded. 73% of notified subjects responded; 70% of nonnotified.

Exposure: 1997 or 50Km Khamisiyah notification; & "exposure" by 2000 plume model

Outcomes: # bed days; activity limitations "attributable to health"; #doctor visits in last 12 mo; #hospitalizations in past 12mo; overall health status (e.g. good or fair); selected medical conditions; selected symptoms; birth defects yes/no; life events scale; PTSD checklist.

Analysis: Chi2 to compare prevalence for notified/non. Cochrane-Mantel-Haenszel test to compute adjusted RRs notified vs non.

Adjustment: exposure or notification status, initial health survey response, age in 1991 (binarized <30 vs >30), gender, race (white or hispanic vs all other; or for exposure, white, afr am, or all other incl hispanic), rank (enlisted vs officer or warrant officer), Army active duty vs Army Reserve or National Guard -- All but 1st two used to compute a propensity score which, divided into quintiles, was used to adjust for these factors in the Cochran-Mantel-Haenszel analysis.

-- No interaction on outcomes noted btn exposure and notification status; so looked at notification separately, adjusted for exposure.

Mahan, Page, Bullman, Kang 2005. Part I. Morbidity Associated with Potential Exposure. Military Medicine 170: 935-944.
Page, Mahan, Kang, Bullman 2005. Part II. Morbidity Associated with Notification of Potential Exposure. Military Medicine 170:945-951

"Khamisiyah" Outcomes

Conclusion:

"There were few adverse health effects associated with notification regarding potential exposure to nerve agents, a finding that contradicts the prevailing view" (not mine!!)

"Those who may be planning future notification efforts may nonetheless take some comfort in the fact that there were few adverse effects seen in this study"

Comment:

Suggests against major impact of suggestibility.

"Khamisiyah" Outcomes

Limitations:

Misclassification potentially severe: bias to the null.

a. Modeling excessively broad and founded on numerous posthoc assumptions; finding of no association, contrast with findings for sarin exposure in Aum Shinrikyo

b. Many in model likely had little or no exposure. Others outside of plume may have had exposure in other CW settings. Contrast prior findings with CW in those at Khamisiyah, vs larger "Khamisiyah" group.

Also: No adjustment for other variables like PB that may account for much of illness, and eliminate excess variability

Mahan, Page, Bullman, Kang 2005. Part I. Morbidity Associated with Potential Exposure. Military Medicine 170: 935-944.

Page, Mahan, Kang, Bullman 2005. Part II. Morbidity Associated with Notification of Potential Exposure. Military Medicine 170:945-951

French Gulf War Veterans

Finding: French PGWV do report symptoms at high rates. No controls

Background:

- 1995: 1st compensation demand for GW problem filed in France.
- June 2000; French Assn of Gulf War Victims (Avigolfe) founded.
- Oct 2000: Working Group in charge of analysis of health data from French GWV created by French govt; rec'd epi study of "all French PGWV in order to describe their complaints & objectively measure their disorders through a standardized clinical examination" [Comment: there is no standardized clinical examination that can objectively measure all disorders]
- Jan 2002: French Ministry of Defense in collab with Ministry of Health solicited the "INSERM" to conduct an "exhaustive investigation of all French PGWV", to "examine self-reported symptom data among GWV; describe main forms of exposure reported in theater; symptoms and diseases that appeared during and after; and determine if unexpected statistical associations of such symptoms could suggest the presence of a new specific syndrome"

Salamon et al 2006. Health consequences of the first Persian Gulf War on French troops. Int J Epi, advanced access published 1-24-06

French Gulf War Veterans

Subjects: all civilian and military personnel who served in the Gulf from 8-90 to 7-91. Based on: census w/in dif milit units btn 00 and 01 by army staff headquarters; list of all decorated GW subjects by Hx Dept of the Army (list created 1991); census of participating organizations for civilians. "Finally, several subjects willing to participate in the study spontaneously contacted us and were added to the list, once we verified their participation in the Gulf War" (suggests lists were not exhaustive)

Design: Survey beginning Feb 02; data collex completed 6-04

Survey: 12-page, self-administered.

- **Exposures**: sandstorms; oil fire smoke; CW or BW alerts; vaccinations; meds.
- **Covariates**: Sociodemog; milit hx; living conditions; dates departure/return; places of operation
- **Health**: diseases and sx appearing B4, during, after the war:
  - Sx: List of 49 symptoms appearing after the mission rated by Hopkins Symptom Checklist. Frequency of sx coded never, <1ce/mo, 1-3x/mo, <1ce a day, daily; except 6 coded yes/no.
  - Diseases: ICD-10-CM used to code self-reported disease
  - Perceived stress: 4 items of Cohen and Williamson Scale
- **Children's health**: miscarriages, @children, diagnoses before & after mission

Salamon et al 2006. Health consequences of the first Persian Gulf War on French troops. Int J Epi, advanced access published 1-24-06

French Gulf War Veterans

Subjects: 5666 French troops deployed by MOD data.

20261 Fr troops deployed by their MOD. Address available for 52% (10,478). Of these 5666 (54%) participated: 2695 Army; 770 Navy; 1895 Air Force; 306 Other branches. Participation rate 28% (5666/20261) and varied by branch: 21% Army to 41% Navy.

Difficult to contact those who retired from army btn 1991 and 2002.

Refusal rate "low" (5% of people contacted by 6-04), mainly due to only briefly present or perceived self in good health. (HOWEVER: loss to f/u may follow opposite pattern)

Mean age 41 at time of participation. Mean duration deployment 118 days, mainly Saudi Arabia 76%; and Iraq 33%; Kuwait 12%.

Primary exposures: Sandstorms 74%; and CW or BW alerts 63%.

Salamon et al 2006. Health consequences of the first Persian Gulf War on French troops. Int J Epi, advanced access published 1-24-06

French GWV: Factor Analysis

Analysis:

Pearson's correlation matrix among the 43 sx coded in 5 levels (excluded Ss with missing values for any sx; and those with no sx)

Principal components analysis: applied to correlation matrix

Retained factors: by Kaiser criterion, Eigenvalues >1; or if factor had at least 2 symptom frequencies that loaded >0.3 on this factor.

Factor loading can be interpreted as correlation coeff measuring the association btn symptom frequencies and the factor

Salamon et al 2006. Health consequences of htefirst Persian Gulf War on French troops. Int J Epi, advanced access published 1-24-06

French GWV: "Bottom Line"

Reported symptoms (total group): though 86% considered selves in good health

Symptom	%	Symptom	%
Headaches	83	Probs with mouth, gums, teeth	29
Sleep difficulty	71	Shortness of breath	27
Irritability	69	Rapid heart rate	25
Backache	63	Depression	24
Memory prob	56	Difficult with speech	23
Fatigue	55	Unintended wt gain >10lb	22
Word finding	53	Loss strength	21
Numbness/tingling	45	Nausea/vomiting	21
Gastralgia	43	Panic/anxiety	19
Joint pain	41	Swollen glands	18
Diarrhea	37	Confusion	18
Muscle pain	34	Shaking	18
Sweats	32	Chem sensitivity	14
Chest pain	30	Slowness healing	8
Rashes	29	Teeth loss	7

Symptom rates: Max in Army; Least in Navy

Salamon et al 2006. Health consequences of the first Persian Gulf War on French troops. Int J Epi, advanced access published 1-24-06

French GWV: Factor Analysis

Factor analysis results (for what it's worth)

7 factors. 1. General; 2. Neurocog/opp resp; 3. Musculoskel vs mood

Factor 1: General, almost all sx load

Factor 2:

a. *Neurocognitive (memory, word finding, confusion, difficulty w speech) orthogonal to:*
b. *Respiratory (wheezing, persistent cough, sore throat)*

Factor 3:

a. *Mood (Depression, panic, anxiety): orthogonal to*
b. *Musculoskeletal (muscle pain, joint pain, joint stiffness, joint swelling)*

Other:

a. *Auditory and tinnitus (load in 5 of the factors)*
b. *Rapid HR and shortness of breath*

Salamon et al 2006. Health consequences of the first Persian Gulf War on French troops. Int J Epi, advanced access published 1-24-06

French GWV

Real Results: High rates sx reporting, no controls

- Higher rates (than other GW studies) of headaches, back pain, sleeping disorders
- Similar rates memory, irritability, fatigue

Limitations:

- Selection/ self-selection: 71% of respondents still in the service (healthy); vs ill may choose to participate; vs ill may not have the energy to fill out a 12 page survey and get it in
- Self-report: recall / reporting bias
- Lack of control group: no risk ratios
- No exposure/outcome associations provided

Salamon et al 2006. Health consequences of the first Persian Gulf War on French troops. Int J Epi, advanced access published 1-24-06

French Gulf War Veterans

Discussion:

"Even if French troops did not face the same exposures as US or UK troops, a "new" symptom cluster, involving disparate organ symptoms, was not highlighted by our analysis" in which "the associations of symptoms were quite similar to those derived among other PGWV and appropriate non-deployed control veterans"

"Until 2000, France did not receive any specific complaints and no study on French PGWV was undertaken" [reminder: absence of evidence is not evidence of absence]

"Fourteen years after the end of the Gulf War it is very difficult to describe deployment circumstances, living conditions, and exposures and to link them to illness"

"Further studies, based on data collected, are in progress and results will be reported in the near future"

Salamon et al 2006. Health consequences of the first Persian Gulf War on French troops. Int J Epi, advanced access published 1-24-06

Incarceration in GWV

Subjects: 3695 Iowa PGWV and nondeployed. 4886 randomly drawn from 1 of 4 groups: GW regular military; GW National Guard / Reserve; nonGW regular Military; nonGW National Guard/ Reserve

Design: Structured Phone Interview of Iowa personnel: PGW and nondeployed

"Outcomes: Sx of medical conditions; psychiatric disorders; health care utilization."

Outcome Here: Incarceration

Result: "GW deployment carried no increased risk of subsequent incarceration overall": rate "lower than nondeployed" (after GWV; higher before GWV) (If were true: like HRT, can't say what true effect of deployment is)

Ever incarcerated: 25.9% GWV; 22.9% nonGWV. BUT: GWV higher pre GW; non higher post-GW; incarceration linked to age at 1990; and no comparison of age in GWV vs nonGWV groups.

Ever incarcerated had higher freq psychiatric and medical comorbidity; and health care utilization.

Associated with male gender; lower education; enlisted rank; lower level milit preparedness; discharge from service; smoking; antisocial traits; having used illegal drugs.

Participation in combat: OR 1.6, (1.0-2.5).

Black 2005. Incarceration and veterans of the first Gulf War. Military Medicine 170: 612-8

"Systematic Review"

Goal: Summarize findings from studies that have assessed multisymptom conditions in GWV and an unexposed comparison group

Method: Studies from jan 1990-May 2004 by search electronic databases.

Included if compared prevalence of chronic fatigue; MCS; CDC GWI; FM; or sx of either fatigue or numbness/tingling in GWV and non GWV. 23 pubs.

Thomas et al 2006. Psychological Medicine X: 1-13.

"Systematic Review"

Condition	#studies	OR	CI .
CFS	10	3.8	2.2-6.7
Fatigue symptoms	16	3.7	2.9-4.8
MCS	7	3.6	2.0-6.2
GWI/CMI (CDC)	5*	3.6	2.8-4.8
Numbness/tingling	6	2.4	1.8-3.1
FM	2	1.8	1.6-2.1

*Duplicated unwin sample

Comment; "The methodological quality of the studies varied but the later and larger studies were of a high methodological standard with robust sampling strategies, adequate response rates and good adjustment for confounders:

Conclusion: "The results support the hypothesis that deployment to the GW is associated with greater reporting of multi-symptom conditions"

Thomas et al 2006. Psychological Medicine X: 1-13.

"Systematic Review"

Goal: Summarize findings from studies that have assessed multisymptom conditions in GWV and an unexposed comparison group

Method: Studies from jan 1990-May 2004 by search electronic databases.

Included if compared prevalence of chronic fatigue; MCS; CDC GWI; FM; or sx of either fatigue or numbness/tingling in GWV and non GWV. 23 pubs.

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"Systematic Review"

Condition	#studies	OR	CI .
CFS	10	3.8	2.2-6.7
Fatigue symptoms	16	3.7	2.9-4.8
MCS	7	3.6	2.0-6.2
GWI/CMI (CDC)	5*	3.6	2.8-4.8
Numbness/tingling	6	2.4	1.8-3.1
FM	2	1.8	1.6-2.1

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Military Deployment & Psychiatric Illness

Finding: Gulf war veterans have a significantly higher prevalence of psychiatric diagnoses with twice the prevalence of anxiety disorders and depression; no signif increase in somatization.

Independent predictors include lower rank, female, unmarried (single or divorced)

Fiedler 2006. Military deployment to the Gulf War as a risk factor for psychiatric illness among US troops. Brit J Psychiatry 198:453-459

Military Deployment & Psychiatric Illness

Subjects: 59% of random sample of 1765 GWV; 51% of random sample of 1832 era veterans.

Design: Phone interview. Administer CIDI interview.

Comment: Positive predictive value of CIDI vs Structured Clinical Interview: ranges .21 for GAD; to .95 for social phobia.

10% of calls monitored, "100% concordance" but not stated to be independent.

Not stated if interviewers blinded to GW status.

Outcomes: Psychiatric conditions by CIDI

Primary Exposure: Gulf War vs Era sample

Fiedler 2006. Military deployment to the Gulf War as a risk factor for psychiatric illness among US troops. Brit J Psychiatry 198:453-459

Military Deployment & Psychiatric Illness

Analysis:

1st pass compare studied groups to total sample; & GWV to era (NDV) (chi-2)

1st pass compare 12-mo prevalence of psych conditions by gender and GW status

Regress on conditions that look different: stepwise forward regression model with inclusion/exclusion of p <. .15 and p > 0.2

Outcomes not regressed (not diff): somatization (fainting, abd pain, menstr problems with other medical explanations "ruled out"!)

Outcomes regressed:

1. Any anxiety d/o including PTSD, GAD, agoraphobia, OCD, panic attack, social phobia
2. Major depression
3. Drug or alcohol dependence

Adjustment variables: race, education, age, marital, active duty status, enlisted rank, other deployments

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Military Deployment & Psychiatric Illness

Results:

Comparability:

"comparable age" but GWV "somewhat younger" (age 39 vs 42). Less educated. Less white. Less married: More enlisted. More active duty.

More never married, 39% vs 29%

Diagnoses:

"Little difference" in rates of:

- Alcohol dependence
- Specific phobia
- Mania
- Somatization

2-3 x increase in rates of:

- Anxiety disorders (the rest)
- Depression
- Drug dependence

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Military Deployment & Psychiatric Illness

Disorder	GWV	Era	NCS (National Comorbidity Survey)*	
Alcohol	4.6	3.1	10.7	
Drug	1.2	0.1	3.8	(increased but RARE)
Major Depr.	15.1	7.8	7.7	
Any Anxiety d/o	16.0	9.7	(not given)	
GAD	6.0	2.7	2.0	
Panic attack	1.6	0.5	1.3	
OCD	2.8	1.1	(not given)	
PTSD	3.4	0.9	5.0	(increased; but <gen pop)
Any psychiatric d/o	26.1	16.1	(not given)	

FINAL MODEL	GW OR	95%CI	Other retained variables
Anxiety	1.8	1.3-2.5	enlisted rank, army, female
Depression	2.1	1.5-2.9	enlisted rank, female, low education
Dependence	Dropped vbl		Other deployment, enlisted rank, male, nonmarried

* NCS: Assessed 12 mo prevalence in adult males

Fiedler 2006. Military deployment to the Gulf War as a risk factor for psychiatric illness among US troops. Brit J Psychiatry 198:453-459

Military Deployment & Psychiatric Illness

Conclusions:

- Depression & anxiety increased
- Low rates of PTSD and of drug/ alcohol abuse
- No material increase in somatization, alcohol abuse

Limitations:

Small samples; low "response rate" (higher "cooperation rate" if reached, 87% and 77%; but more if white, noncommissioned and warrant, commissioned officers; signif dif age, gender, branch by response rate)

CIDI a limitation -- if you believe DSM better

Observation: Rates elevated in conditions (depression and anxiety – conditions with very high cross-correlation generally > 0.5) that have somatic symptoms (e.g. fatigue, sleep, concentration) in diagnosis: interesting to look separately at psychic vs somatic symptoms

Fiedler 2006. Military deployment to the Gulf War as a risk factor for psychiatric illness among US troops. Brit J Psychiatry 198:453-459

PB & sarin: effects on Ach levels in brain

Conclusion: no long term effect on choline and acetylcholine when average across brain regions

Subjects: male Sprague Dawley rats 250-300g

Design: PB, sarin, both or neither x 3 weeks; then sacrifice animals at 2, 4, or 16 weeks thereafter

Exposure:

PB: 80mg/L in drinking water vs tap water x 3 weeks: or tap water control

Sarin: 62.5 microgm/kg injex 3x/week x 3 weeks; or saline injection control

	Sample Size		
	2 weeks	4 weeks	16 weeks
Group 1: neither		11	10	8
Group 2: PB	10	12	9	
Group 3: Sarin	12	12	8	
Group 4: both	12	10	7	

Send by air freight 1 week prior to sacrifice

Then pulse injection of radiolabeled choline just before sacrifice; with microwave fixation of the brain 1 minute later

Shih 2006 Cerebral acetylcholine and choline contents and turnover following low dose acetylcholinesterase inhibitor treatment in rats. Arch Toxicol.

PB & sarin: effects on Ach levels in brain

Accessory outcome: signs of cholinergic toxicity: fasciculation, tremor, convulsions, salivation, lacrimation, eyebulb protrusion, general activity and coordination

Outcome: Gas chromatography mass spectrometry for brain regional measure of:

1. Brain (tissue) ACh;
2. Brain (tissue) choline;
3. *Choline as measure choline uptake from the blood (labeled ch)
4. *ACh as measure of Ach turnover (labeled ACh)

Measured of these in HC, infundibulum, mesencephalon, neocortex, piriform cortex, and striatum at baseline; then change value

AChE inhibition: Did NOT measure AChEi; but reportedly prior study showed 49% inh with PB; 66% inh with sarin; 73% inh with both

Analysis: ANOVA for brain factors "region" and "Treatment"; Tukey Kramer multiple comparison test if signif

ANCOVA: using the region's values for each variable as covariates

Shih 2006 Cerebral acetylcholine and choline contents and turnover following low dose acetylcholinesterase inhibitor treatment in rats. Arch Toxicol.

PB & sarin: effects on Ach levels in brain

Result:

0. No cholinergic toxicity signs (also: no msr AChE inhib)
1. Regional differences in the outcome variables
2. No treatment/region interaction
3. No duration/region interaction
4. Treatment differences:

-- At 2 then esp 4 weeks: increase ACh in sarin groups (signif less if both); increase Ch signif only if both

-- At 16 weeks: trend decrease ACh in sarin group (looks similarly large, but not signif); trend increase choline uptake in PB group (NS)

Shih 2006 Cerebral acetylcholine and choline contents and turnover following low dose acetylcholinesterase inhibitor treatment in rats. Arch Toxicol.

PB & sarin: effects on Ach levels in brain

Limitation:

1. No msr AChE inhib; not clear how close to 1st signs
2. Looks only at choline and Ach (even then very small samples)
3. To look at cholinergic function: need to include many other elements including amount ACh per vesicle, number vesicles released in a signaling event; nicotinic and muscarinic Ach receptor density by type and brain region and time (and coexposure), binding affinity, receptor sensitivity;
4. Small sample sizes even for the measures used: trends esp at 16 weeks, maybe signif with larger sample?
5. Changes appear to be evolving (including reversing) with time; need to look further out in time
6. Single size, gender; single species (not human)

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