

Presentation 16 – Beatrice Golomb

**Review of Recent (and recently identified)
Gulf War Research**

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R₁

Epidemiology

R₂

Australian 2003

**Ss: 1456 GWV of all 1873 asked. 1588 comparison
rdmly selected from Australian Defence Force that
were Gulf eligible but not deployed. Queried 4-02.**

**Outcomes: Mental health SF12 and GHQ12.
Physical health SF12. Functional impairment. # sx
reported from ~61 questions.**

**Signif exposures: ≥ 10 immunizations. PB tabs.
Pesticides/insecticides. Being in a CW area.
AntiBW tablets. Stressful milit svc experiences.**

R₃

Australian 2003

More Findings:

- ↑ neuropathic sx (no dif in neuro exam): assoc
with PB, solvents, pesticides, antimalarials, and
immunizations.
- ↑ CFS & all fatigue-related health outcomes
- No ↑ birth defects

R₄

Australian 2003

| | Dif in Phys. | Dif in Mental | OR #sx | OR Fcn† |
|--------------------|--------------|---------------|--------|---------|
| Vaccine dose resp: | -0.5* | -0.4* | 1.04* | 1.1* |
| PB: dose resp: | -1.2* | -0.7 | 1.1* | 1.4* |
| PB: any vs none | -2.5* | -2.0* | 1.4* | 1.8* |
| PB: > 250 tabs | -3.4* | -1.3 | 1.4* | 2.5* |
| CW area: | -3.7* | -4.3* | 1.3* | 1.4* |
| Pesticides: | -3.4* | -3.4* | 1.3* | 1.5* |
| AntiBW tabs: | -2.3* | -2.7* | 1.4* | 2.1* |
| Repellents: | -1.1 | -0.5 | 1.2* | 1.4* |
| DU: | -0.2 | -0.1 | 1.0 | 1.1 |
| Deployment time‡ | -0.4 | -1.4* | 1.1* | 1.2 |

Phys and mental fcn from SF12. # sx from 61 sx queried.
 †Functional impairment during the past 2 weeks
 ‡Deployment not completed before air war

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Australian 2003

| | Phys. | #sx | Fcn† | Mental |
|--------------------|--------|-------|-------|--------|
| SF-12 | | | | |
| Vaccine dose resp: | < .001 | <.001 | <.001 | .001 |
| PB: dose resp: | < .001 | <.001 | <.001 | .068 |
| PB: any vs none | < .001 | <.001 | =.004 | .012 |
| CW area: | < .001 | <.001 | <.001 | <.001 |
| Pesticides: | < .001 | <.001 | =.013 | <.001 |
| AntiBW tabs: | = .001 | <.001 | =.01 | .002 |
| Repellents: | = .055 | =.001 | =.025 | NS |
| DU: | = .718 | =.939 | .617 | .947 |
| Deployment time ‡ | =.469 | .051 | =.202 | .043 |

Phys and mental fcn from SF12. # sx from 61 sx queried.
 †Functional impairment during the past 2 weeks
 ‡Deployment not completed before air war

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Hotopf 2003: GWI better worse or same

Sample: 1245 GW: Compared to 698 Bosnia; 734 Era veterans. Stratified sampling from prior survey, based on severity of fatigue.

Outcome: self reported fatigue, Chalder fatigue scale; GHQ psych distress; SF-36 phys fcn & health perception; count of physical sx -- all are compared to response in 1997 (then N = 8196).

Finding: GWV continued to experience poorer health on all outcomes. Era vets showed lower incidence of fatigue; GWV show more persistence of fatigue than either comparator.

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Hotopf 2003: GWI better worse or same

Finding:

-GWV continued to experience poorer health on all outcomes: GWV Bosnia Era

| | | | |
|------------|------------|------------|------------|
| SF-36 phys | 90.3->88.7 | 95.4->92.9 | 92.1->90.8 |
| SF-36perc. | 65.8->65.9 | 76.2->72.9 | 76.8->74.4 |
| GHQ case | 14.5->14.2 | 13.1->13.2 | 12.4->12.9 |
| Fatigue | 17.8->16.9 | 15.6->15.3 | 14.7->14.9 |
| Tot #sx | 11.0->10.7 | 6.2->7.9 | 5.3->6.4 |

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Hotopf 2003: GWI better worse or same
Incidence (I) and Persistence (P). Adjusted OR

| | GWV | Bosnia | Era |
|---------------|-----|--------|------|
| Fatigue>3 (I) | 1.0 | 0.9 | 0.5* |
| Fatigue>3 (P) | 1.0 | 0.7* | 0.7* |
| GHQ >2 (I) | 1.0 | 0.9 | 0.7 |
| GHQ >2 (P) | 1.0 | 1.1 | 0.6* |
| PTSD case (I) | 1.0 | 0.8 | 0.9 |
| PTSD case (P) | 1.0 | 0.8 | 1.2 |

GHQ as index of “psychological distress”
 Adjusted for: age, sex, rank, marital status ^{R₉}

Hotopf 2003: GWI better worse or same
Incidence (I) and Persistence (P). Adjusted OR

| | Era | Bosnia | GWV |
|---------------|-----|--------|------|
| Fatigue>3 (I) | 1.0 | 1.8 | 2.0* |
| Fatigue>3 (P) | 1.0 | 1.0 | 1.4* |
| GHQ >2 (I) | 1.0 | 1.3 | 1.4 |
| GHQ >2 (P) | 1.0 | 1.8 | 1.7* |
| PTSD case (I) | 1.0 | 0.9 | 1.1 |
| PTSD case (P) | 1.0 | 0.7 | 0.8 |

GHQ as index of “psychological distress”
 Adjusted for: age, sex, rank, marital status ^{R₁₀}

UK Gulf Mortality Data*
GW cohort: 53,409.
Era comparators: 53,143 similar age, gender, svc, rank in service Jan 1 1991 but not deployed
Outcome: deaths reported in service till Dec 31,2003
Finding:

- All deaths 0.98 (0.88-1.09)
- Disease-related death 0.82 (0.70-0.97)
- Infectious and parasitic: 1.99 (0.43-12.3)
- External injury & poisoning: 1.15 (0.99-1.35)

^{*}www.dasa.mod.uk/natstats/natstats.html ^{R₁₁}

Stability of recall of hazards over time*

Sample: 1245 GW; 698 Bosnia; 734 Era veterans stratified sampling from first survey based on severity of the fatigue and gender.

- Bosnia & GW ↑, on ave, #exposures recalled over time.
- Improved health perception was associated with ↑ “forgotten” (no longer endorsed) exposures; while worsening health perception was associated with new endorsement of exposures in Gulf but not Bosnia cohort.
- Some exposures were recalled more reliably than others, e.g. smoke from oil fire, handle prisoner of war, small arms fire, scud exploding w/in 1 mi, and seeing dismembered bodies (GW). Gulf had ↑test-retest reliability vs Bosnia.

Wessely et al Br J Psychiat 2003;183:314-22 ^{R₁₂}

Stability of recall of hazards over time*

- Those remaining in service were most likely to no-longer-endorse exposures, both groups.
- No-longer-endorsed is related to health perception & PTSD (not phys health or GHQ) in GWV; & to Phys health & PTSD in Bosnia.
- Newly-endorsed hazard NOT related to phys health in GWV, but was related to health perception, GHQ, PTSD (all include mental health); & related to PTSD only for Bosnia.
- Exposure vbls did not include PB; or anthrax vaccine, e.g.
- There was no assoc of exposures to health levels: phys, psychol, PTSD --but miss exposures like PB which could confound relation of other exposures

Wessely et al Br J Psychiat 2003;183:314-22

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Exposures, stressors & life events

Hallman's "high symptoms" vs "low symptom" GWV were more likely to report, after adjustment (not all listed):

- BT vaccine 1.78, p = 0.02
- Anthrax vaccine 1.72, p = 0.03
- Chemical/biol warfare p < 0.01
- Days taking any PB pills, 12.0 vs 9.3%, p = 0.07
- Days taking > 3 PB pills, 3.3 vs 2.0%, p = 0.08
- Days gas mask worn ≥4hrs, p < 0.01
- Wounded, p < 0.01
- Physical deprivation, p < 0.01
- "Food/infections/equipment" p < 0.01
- "Mistrust in military (.01), traumatic event (.03), "desert/exhaust (<.01)

*Adjust: age,gender, race, educ, milit branch,rank,duty,marital status, self-reported health @deployment, alcohol, smoking, illicit drug use, PTSD sx
Boyd KC, Hallman WK et al 2003. J Occup Env Med 45:

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Symptom patterns in Registry GWW

Design: mail survey completed by 1161 Registry GWW

84.5% of respondents believed they had med problems attributable to GW service;

5.3% did not answer. (~10% did not believe they did.)

Symptom list: 48 symptoms grouped by organ

*Hallman, W.K., et al., *Symptom patterns among Gulf War registry veterans*. Am J Public Health, 2003. 93(4): p. 624-30.

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Symptom patterns in Registry GWW

Exploratory factor analysis: 4 symptom factors.

1. Mood/memory/fatigue
2. Musculoskeletal
3. Gastrointestinal
4. Throat/breathing

K-means cluster analysis: 2 groups

1. Healthier, 60%: ave 18 sx; 33% mod, 11% severe
2. Sicker, 40%: ave 37 sx, 40%mod, 35% severe

Cluster 2 more likely to have ≥1 of 24 medical conditions

- Includes FM, IBS, MS, CFS, depression, PTSD, bipolar, anxiety d/o, thyroid disease, DM, sterility. Hay fever, TB, eczema/psoriasis appear less frequent.

*Hallman, W.K., et al., *Symptom patterns among Gulf War registry veterans*. Am J Public Health, 2003. 93(4): p. 624-30.

R 16

Cancer in UK GWV

Sample: N=51721 GWV; N=50755 era cohort “matched” for age, sex, rank, service, level of fitness who were not deployed

Outcome: Incident Cancer

Finding: No difference in cancer.

270 GW, 269 Era cancers: Incidence RR 0.99 (.83-1.17)

Limitation: less health chosen for nondeployment & hx of illness/drugs/exposures causing or resulting from illness?

Conclusion: No evidence of excess cancer to date; merits continued follow-up due to long latency for cancers

Macfarlane GJ 2003, BMJ 327:

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Factor Analysis of Fatiguing Sx

Sample: 640 GWV with FS; 5417 GWV and 6493 nonGWV not meeting criteria & w/o exclusionary conditions. From Han Kang's 15K GWV/15K nonGWV

FS = fatiguing symptoms by 1994 mod CDC criteria x chronicity.

Excess fatigue (mild/severe) first appearing in or after GW; no swelling in any joints; at least 4 of 8 sx 1st appearing in or after GW among a set; and none of a set of conditions including DM, endocrine, seizures, neuralgia, etc.

SX (4 of 8): headache, sore throat, swollen glands, muscle or joint aches/pain/cramps, fatigue lasting >24 h after exertion, awaking tired after full night sleep, difficulty concentrating/memory loss.

-- Of 11,441 GWV questionnaires, 5.6% met these criteria

Analysis: Factor analysis done separately in each group; factor correlations examined

6 subgroups/factors: named: fatigue, pain, infectious, GI, resp, & neurolog/mood/fatigue

Similar factors for each group: BUT lower interfactor correlations in GW vs control groups, lower for 13 of 15

Young HA et al 2003 J Occup Env Med 45(12)

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Factor Correlations Are Lower for GW-FS

| | Fatigue | | |
|------------|-----------------------|-------------------------|----------------------------|
| | <u>GW_FS</u> n=582 | <u>GW_ctl</u> n=5076 | <u>NonGW_ctl</u> n=6222 |
| GI | .24 | .40 | .33 |
| Resp | .13 | .34 | .27 |
| Neuro | .55 | .88 | .81 |
| Infectious | .14 | .33 | .38 |
| Muscskel | .08 | .50 | .40 |

*Also lower for the other factors with each other

Young HA et al 2003 J Occup Env Med 45(12)

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Factor Correlations Are Lower for GW-FS

Inference: More differentiated factors in GW FS group c/w distinctive set of underlying pathogenesis assoc with the factors in that group BUT subtle difs btn groups in symptom factor structures, e.g., is another possible reason. **ALSO:** can depend on the specific list of sx included on the questionnaire.

Importance: Different groups may have different pathogenesis and response to treatment. This approach may or may not help to differentiate such groups.

Young HA et al 2003 J Occup Env Med 45(12)

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Chemical Exposures Including AChEi

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Chemical Mixtures

1. PB± DEET± Permethrin causes sensorimotor deficit & change in brain AChE activity (rats).
 - Affect: AChE activity; ligand binding m2; ligand binding nicotinic rec, differ by combination and brain region. But chronic impact (after d/c exposure) not evaluated.
2. Stress + low dose chemicals damage brain areas even w/o BBB disruption (rats):
 - Some brain regions show BBB disruption (cingulate cx, dentate gyrus, thalamus, hypothalamus).
 - Regions w/o e/o BBB disruption also show effects: ↓AChE activity, ↓M2 binding midbrain/cbellum; assoc. w/ signif neuron death, ↓microtubule-assoc pr, ↑glial fibrillary acidic pr (cereb cx, HC: CA1 & CA3).

- 1. AbouDoria et al 2004. Pharmacology, Biochemistry & Behavior 77: 253-262
- 2. Abdel-Rahman A et al 2004. J Toxicol & Environ Health A 67: 163-192.

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AChEi: 2 sentinel patients with delayed sequela

- Case 1: 1982 IMPF & PB exposure -> myalgia & fatigue (isopropyl methylphosphonofluoridate inhalation). From 1993 developed fatigue, aches, pains esp after physical activity; also ↑CK. Nonspecific myopathy diagnoses with ragged red fibers. ↓ in concentration, memory, verbal fluency, ability to plan & initiate activities, comprehension of abstract concepts; easy distraction. Also: severe pain, digestive difficulties, weakness.
- Case 2: 1982 IMPF & PB exposure (60mg tid x 6 mo for prophylaxis) + heat stress. From early 1990s, noted myalgia, mild neuropathy, cognitive impairment, difficulty concentrating, mood alterations and chronic fatigue. Able to do sedentary work, only 3-4h/d. CK elevation noted 1999-Jan 2003.

- Friedman L S et al 2003. CK elevation & signal muscle damage following exposure to anticholinesterases: 2 sentinel patients. Arch Environ Health 58:167.

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Illness Mechanisms & Markers

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Sympathetic/ Parasympathetic differences

1. Females w/ FMS or GWI show robust ↓ in HRV vs Female controls or Males (including pts) - ↓ parasymp modulation of HR. Other difs possible but small sample, n=5-19 per group.
 2. Pts w/ CMI (chronic multisystem illness, including GWI) have ↑ catecholamine levels, Epi & esp NE, vs controls. ↓ NE response to stressor with submaximal exercise test.
- 1. Stein PK 2003, Gender Effects on Heart Rate Variability in fibromyalgia and Gulf War Illness. 7 M GWI, 5 F GWI, 19 M control, 18 F control
 - 2. Olivadoti 2003. Catecholamine responses to standardized stressors in chronic multisystem illnesses. N=53 case (5 FM, 11 CFS, 22 both, 15 GW), 36 control

R 25

Enhanced sensitivity to pain

Subjects: 12 GWV with abd pain & diarrhea s/p neg workup developed during PGW. 7 civilian & 5 veteran controls.
Exposure: a) rectal distension (35 & 55mm) & b) hot water R foot & hand (35° & 47°C x30sec)
Outcome: visual analog scale pain intensity & unpleasantness, 2 trials each
Finding: p < 0.001 higher rating of pain intensity and pain unpleasantness for both exposures
Conclusion: visceral hypersensitivity in PGWV with abd pain/diarrhea sim to that shown with irritable bowel. Also: cutaneous hypersensitivity “and higher levels of anxiety and somatic focus accounting for these differences in pain reporting” (no, attending them!)

Dunphy RC et al 2003, Pain 102: 79-85.

R 26

fMRI analysis of pressure pain

Subjects: 7 GWV pts, 7 FM pts, 7 healthy controls
Exposure: painful pressure to L thumb by “random staircase”; determine stimulus needed to evoke subjective mild, moderate, or intense pain. 25s blocks of painful pressure & release during 10 min fMRI sessions.
Outcome: fMRI. Pressure pain intensity.
Findings:
1. GWV&FM had ↑ pressure pain sensitivity & subjective levels (p < .05).
2. In all groups, subjective intense pain was assoc with contralateral 1° somatosensory cortex, insula, bilat. 2° somatosens cx, ipsilateral cerebellum activations. Both patient groups (only) showed activation in inf. frontal gyrus and hypothalamus not seen in controls. GW uniquely lacked activation in amygdala.
Conclusion: GWV like FM have altered pain processing: signs of pain augmentation; cerebral activations evoked by less stimulus; unique frontal and thalamic responses.
Grant M.A.B., Clauw D.J., fMRI analysis of pressure pain in Gulf War Illness, FM, and Healthy control subjects. (abstract)

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