Presentation 16 – Beatrice Golomb

Review of Recent (and recently identified) Gulf War Research

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R 1

Epidemiology

R 2

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.

R 3

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

R 4

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

R 5

Australian 2003

SF-12	Phys.	#sx	Fcn†	Mental
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

R 6

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.

R 7

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

R 8

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

R 9

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

R 10

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

R 11

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

R 12

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

R 13

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:

R 14

Symptom patterns in Registry GWV

Design: mail survey completed by 1161 Registry GWV

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.

R 15

Symptom patterns in Registry GWV

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 Gluf 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

MacfarlaneGJ 2003, BMJ 327:

R 17

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)

R 18

Factor Correlations Are Lower for GW-FS

		Fatigue	
	GW.FS	GW.ctl	NonGW.ctl
	n=582	n=5076	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)

R 19

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)

R 20

Chemical Exposures Including AChEi

R 21

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

R 22

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, diffficulty concentrating, mood alterations and chronic fatigue. Able to do sedentary work, only 3-4h/d. CK elevation noted 1999-Jan 2003.

- Friedman LS etal., 2003. CK elevations signal muscle damage following exposures to anticholinesterases: 2 sentinel patients. Arch Environ Health 58:167.

R 23

Illness Mechanisms & Markers

R 24

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 10min 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)

R 27