Presentation 16 – Beatrice Golomb

Update on Research in Persian Gulf War Veterans

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EPIDEMIOLOGY

Australian factor analysis

SS: 1322 male GWV from whole cohort of 1871 Australian GWV; VS 1459 male era Australian Defence Force controls, from 2924 stratified random sample of 26,411 era personnel

Data: 63 self-reported symptoms; sz in last 1mo omitted due to low prevalence; Queried non, mild, mod, severe.

Analysis: Factor analysis of polychoric correlations

Polychoric: resp categories "none" "mild" etc presumed to be in a continuum with threshold for transition; continuum presumed Gaussian with overlap; Polychoric correlation coefficients are the bivariate correlations btn two such underlying continua derived by an iterative procedure. Reportedly robust to skewed nonnormal distributions of the underlying continua.

Australian factor analysis

Factor 1	Factor 1, cont'd	Factor 2	Factor 3
Psychophysiologic		Cognition	Muscular
Vomiting	Sore throat	Loss concentration	Stiffness several joints
Stomach cramp	Flatulence/burping	Feeling distant	Pain sev joints
Diarrhea	Bowel/bladd ctrl	Unrefreshing sleep	Gen muscle ache/pain
Indigestion	Burning sex organs	Forgetful	↓Sensation hands/feet
SOB		Loss interest sex	Low back pain
Dry mouth		Sleep problems	Tingling/burning hands/feet
Feel feverish		Avoid situations	
LN swelling		Easily startled/jumpy	
Persistent cough		Sex dysfcn	
Pain on urination		Distressing dreams	
Constipation		Fatigue	
Trouble speaking		Irritability/anger outburst	
Dizzy, faint, blackout		Word finding. Disoriented.	
Loss balance/coordination		Sensitive to noise; light; smells	

Forbes et al 2004 Occup Environ Med 61: 1014-1020

Australian factor analysis

Factor Rotation

- Factors: items internally intercorrelated; but anticorrelated with one another
- Varimax: goes for orthogonal solutions
- Promax: allows oblique I.e. correlated solutions
- How many Factors to retain: chosen by examination of eigen values (crudely amount of variation accounted for by each factor)
- Arbitrary "but conventional" threshold of 0.4 chosen for factor loadings (I.e. retain items with loadings >0.4 in each factor)

Forbes et al 2004 Occup Environ Med 61: 1014-1020

Australian factor analysis

Factor Analysis: Split halves sample:

Split to random halves & obtained factor structure in each

2, 3, and 4-factor solutions obtained for each; congruence of the solutions by Pearson product-moment and one-way random-effects intra-class correlation coefficients

Validation:

Construct validity by correlate PCS-12, MCS-12 of SF-12

Internal consistency of each factor by Cronbach's alpha

Intraclass correl coeff to see if factor loading sim in GW & comparison group

Invariance of obtained solution for GW & comparison gp

Forbes et al 2004 Occup Environ Med 61: 1014-1020

Australian factor analysis

Result: 3 factor solution. 41% of variance by 1st factor; then 3.3, 2.7; then 1.9, 1.7%

Scree plot of Eigenvalues on vertical axis and factor number on horiz; dominant 1st factor with possible contributions by 2 others, rest look like detritus (scree)

Factor 1: "Psychophysiological distress"

Factor 2: "Cognitive distress"

Factor 3: "Arthroneuromuscular distress"

Promax did better: more interpretable and distinct factor solutions with nonorthogonal than orthogonal Varimax: The underlying factors were moderately correlated

Forbes et al 2004 Occup Environ Med 61: 1014-1020

Australian factor analysis

Similar factors in era controls -- not very informative.

- Conditions with ANS problems (whether DM or Shy Drager) will cause many ANS sx
- Conditions disrupting sleep -- e.g. OSA or depression -- will produce factor 2 symptoms
- Conditions producing widespread musculoskeletal pain: whether FM or statins or metabolic myopathy -- will cause the items in factor 3

Even if items within each factor are not always correlated there will be enough that are correlated from these sources to provide the factor structure...

Forbes et al 2004 Occup Environ Med 61: 1014-1020

PGW ALS Replication Study

Rationale: concern about case-ascertainment bias in prior GWV studies: GWV may have all been captured but nonGWV may have had less motivation or knowledge. Capture-recapture.

Coffman, Horner et al 2005. Estimating the occurrence of ALS among Gulf War (1990-1991) veterans using capture-recapture methods. An assessment of case ascertainment bias. Neuroepidemiology 2005: 24:141-150

PGW ALS Replication Study

Method:

A. Sample ALS by several approaches.

1. VA database
2. DoD database
3. Phone-line database (toll-free number)
4. ALS assn database (survey by natl ALS assn).

B. Cross-check list 3 ways to gauge differential undercount of ALS in nondeployed (to model fraction missed in both groups): log linear model; sample coverage; ecological models

Coffman, Horner et al 2005. Estimating the occurrence of ALS among Gulf War (1990-1991) veterans using capture-recapture methods. An assessment of case ascertainment bias. Neuroepidemiology 2005: 24:141-150

PGW ALS Replication Study

Result: Though all showed *modest* differential undercount of ALS in nondeployed, there remained an age-adjusted increase in ALS among those deployed to SW Asia in 1991 PGW.

Comment: VA database: deployed & nondeployed listed at similar rates (72% of deployed, 71% non)

DoD database: nondeployed are listed at slightly higher rate (72%); & deployed cases at a lower rate (45%) than overall population percent (62%)

Coffman, Horner et al 2005. Estimating the occurrence of ALS among Gulf War (1990-1991) veterans using capture-recapture methods. An assessment of case ascertainment bias. Neuroepidemiology 2005: 24:141-150

RISK FACTORS

Anthrax: Canadian Forces

Finding: anthrax vaccine did not cause health problems in Canadian post-GW personnel

Actually: With two samples not comparable at baseline, who were deployed at different times to different places, there were not large differences in change rate for fraction-of-total dx (and sx codes) for each among a set of most common dx and sx codes -- based on chart abstraction (not active inquiry).

Symptom rates were not actively elicited.

Hunter D 2004 Military Med 169 (10) 833
Health effects of anthrax vaccination in Canadian Forces

Anthrax – Canadian Forces

SS: N = 848 total, actively deployed
Of 1143 identified for study: 571 vaccinated; 572 randomly selected from larger group of 1655 not.

- AVA exposed: Gulf-deployed; Feb-May 98
- Control unexposed: Kosovo-deployed Jun-Dec 99

Anthrax vaccine Exposure:
Lot 010-1 from BioPort; 3 inoculations on or about Mar 15, Mar 30, Apr 15 1998

Other systematic exposure differences: Time of deployment. Place of deployment.

Anthrax – Canadian Forces

Design: "quasi-experimental" retrospective chart review.
(Collect data for 4.5 years; but confine analyses to 8mo since comparison group deployed later, don't have f/u for whole group beyond 8mo)

Comment: A quasi-experiment involves assignment (intervention vs control) without randomization. But here: the groups systematically differ in two other ways.

Anthrax - Canadian Forces

Outcome: % change in frequency of dx & sx rates by chart abstraction between the 12-mo period before deployment and the 8mo period after deployment

BUT states: rates were calculated by "dividing the number of events (e.g. diagnoses) for specific codes by the total number of events [sic] and multiplying by 1000" – vs by person-time!!
Thus Sx 1 can "↑" just b/c Sx 2 ↓d (so fraction rises)
Also: AVA acute AE may have been included in predeployment diagnosis.

Anthrax - Canadian Forces

Sx-Dx procurement:

ICD-10-CA codes from chart review abstraction blinded to vaccination status: Each charted diagnosis, symptom, or injury

Chart retrieval rate: 86% control, 82% vaccinated: some charts not provided by Canadian Forces: 12 not found; 125 not available since "in movement" or currently deployed; 27 required for current treatment.

Anthrax - Canadian Forces

Result:

•Not wholly comparable at baseline

	Anthrax	Not
Age 35-44	**26%**	**14%**
Age 45-54	**1.5%**	**1.8%**
Women	**4.8%**	**8.5%**

Anthrax - Canadian Forces

Result:

Not wholly comparable: Different top **diagnoses**

Top dx, PGW (Anthrax vaccinated)

- Disorders of refraction & accommodation
- Soft tissue d/o related to use overuse & pressure

Top dx, Kosovo (not vaccinated)

- Acute URI of multiple & unspecified sites
- Other disorders of muscle
- Soft tissue d/o related to over/use & pressure

Anthrax - Canadian Forces

Sx decreased in AxVax-- incl those likely related to vaccine. Deployment effect? Vaccine predepl?

Result:	Anthrax vax	No vaccine	p
# symptoms: later values are % of these numbers			
	2653pre->1712post	**2689pre->2054post**	
% of symptoms caused by:			
- **Localized swelling, mass & lump of skin** & subcutaneous tissue	5.7->3.3,-2.4	3.8->3.4, -0.4	.01
- Other skin changes	6->3.3, -2.7	5->5.3, +0.3	0.00

Anthrax - Canadian Forces

Diagnoses: Pre-post change as fraction of that groups total dx. Not much difference by these categories. Selected findings:

Result: Ax change

•D/o of refraction & accommodation
-1.9% vs -0.2%, p = 0.08

•Tissue disorders related to use, overuse & pressure
+0.3% vs -1.6%, p = .627

•Soft tissue disorders related to use, overuse, pressure
+0.6% vs +2.3%, p = 0.115

Anthrax - Canadian Forces

Result:	Anthrax vax	No vaccine	p
Disturbance of skin sensation			
	4.9->3.2, -1.7	3.4->3.9, +0.5	0.00
Abd/pelvic pain			
	3.5->3, -0.5	2.8->3.1, +0.4	.069
Other S&S involving digestive system & abd			
	3.7->3.2,-0.5	3.4->3.9, +0.5	.048

BUT as these go down in vaccine group as % of total sx, something else is going up -- as a %.

Anthrax - Canadian Forces

Concerns: bias & confounding

- Diff populations: not comparable @baseline in demographics; not comparable at baseline in proportion of prior diagnoses
- Systematic differences in "treatment" unrelated to anthrax vaccine:

Why not call it a quasi-experiment of deployment place and time (secular trend)?

- Small N: But larger N would not overcome bias
- Says change rate: but as % of events!!

Anthrax - Canadian Forces

Concerns:

- Sx DUE TO vaccine may have amplified predeployment rates: Note high rate of "localized swelling, mass and lump of skin and subcutaneous tissue" before deployment for vaccine vs control group, "decreased" after deployment

MARKERS

Markers

HEART RATE VARIABILITY

- SS: FM N=26 ; 19 FEM
- GWI N=11; 5 FEM
- HEALTHY N=36; 18 FEM

ASSESSMENT: HRT 24°; DAY; NIGHT

RESULT:

HEALTHY CTRL: MALE=FEM

GWV & FM: HRV DECREASED IN FEM

BUT: that's not quite the whole story:

Stein, ... , Clauw 2004. Am Coll Rheumatol 51(5): 700-8

HRV = hrt rate variabil; HR = heart rate; SDNN = SD of nl to nl intervals; ULF = ultra low frequency; SDNNDIX = age □SD of nl to nl interval over 5 minutes; pNN50=% normal to nl intervals >50ms dif from prior; rMSSD = root mean square dif btn successive nl-to-nl intervals; VLF = very low freq; LF = low freq; HF = hi freq

Markers: HRV (Stein 2004)

GW > FM>CTRL: GW ALWAYS MORE DIFFERENT- E.G. 24° HRV

		GW	FM	CTRL
Long term HRV:				
• Hi HR bpm	.065	76	74	70
• low SDNN	.056	117	125	140
• Low n ULF power:	NS	9.19	9.24	9.41
Intermed term HRV:				
• Low SDNNDIX:	.056	53	63	68
• Low Ln LF power	.054	7.2	7.5	7.7
• Low Ln LF ratio	.050	6.4	6.9	7.0
Short term HRV				
• Low pNN50(%)	.023	7	13	18
• Low rMSSD (msec)	.036	27	37	43
• Low Ln HF power	.044	5.2	5.9	6.1

P-values for analysis of variance

Markers: HRV

- **Diffs are even more extreme for women: 24°, Day, & night**
- **Intermed term HRV: GWV women are signif different from FM women despite N=5 in female GWV group.**
- **Most GWV HRV are signif dif from normal, despite small N**
- **FM differs from Ctrl & GWV : Only for FM are ratio-based HRV items NOT different for men vs women**
- **In contrast, the remaining HRV factors show M-F differences in GWV and FM but not control**
- **∴ GWV shows both different pattern; and different quantitation than either FM or control (small N, needs replication)**

P-values for analysis of variance

Stein PK, ... , ClauwDJ 2004. Arthritis and Rheumatism 51(5):700-8

Markers: EMG with PN symptoms

- Decreased prevalence of peripheral nerve pathology by electrodiagnostic testing in Gulf War veterans
- Ss: 56 GWV and 120 nonGW referred to EMG lab, Walter Reed. Consecutive GW referrals 1994-5.
- NonGWV med records randomly chosen from retained med records of persons referred in same time.
- GWV ~ older (39 vs 36); fewer females (6 v 62%)
- More radiculopathy in nonGWV (p = 0.000 for active duty males; and for all). No diff peripheral or compression neuropathyPasquina 2004. Military Medicine 169: 11

Markers: EMG with PN symptoms

- Another difference from the civilian population: AMONG THOSE citing sx that lead to referral for EMG, fewer have postivie electodiagnostic testing.
- They interpret this as lower threshold for referral.
- These people still have sx; the question is, what is the origin? (lower pain threshold? Other abnormality?)

Pasquina 2004. Military Medicine 169: 11

Markers: EMG with PN symptoms

- Not known true; can't r/o a higher threshold.
- It is equally consistent with higher prevalence of a distinct cause for these sx that does not show up on electodiagnostic testing; or that amplifies sx for the same degree of subevident pathology. EMG may be another marker that, statistically, distinguishes GWV with similar symptoms.

Pasquina 2004. Military Medicine 169: 11

Markers: flow resp to Ach iontophoresis

- Finding: Exaggerated response of bloodflow to ACh iontophoresis in CFS vs controls; but NOT in GWV; and NOT in persons with fatigue associated with occupational exposure to OP pesticides.
- Another factor distinguishing GWV from the mass of CFS & fibromyalgia patients – and rendering them similar to OP cases.

Pasquina 2004. Military Medicine 169: 11

Markers: Ach iontophoresis

Subjects:

- CFS N=53 (randomly selected from prev studied group with dx of CFS). Excluded 6 with DM, angina, other.
- GWS N=24 (from registry)
- Post-Organophosphate: N=25 (Hx ill health from definite OP exposure; from registry)
- Healthy control: N=40, matched on age, sex for each group

Pasquina 2004. Military Medicine 169: 11

Markers: Ach iontophoresis

Marker: blood flow response to iontophoresis of Ach and methacholine challenge

Iontophoresis = drug delivered on arm, dissolved in water, through administration of current. Laser doppler imaging to assess cutaneous perfusion.

Outcome: median laser doppler flux over delivery site.

Result: GWV differ from CFS; same pattern as OP.

- Signif ↑ bloodflow resp to ACh in CFS (p = .029).
- Normal (no ↑) in GWS & OP-exposed

Pasquina 2004. Military Medicine 169: 11

Markers: Pulmonary Function

Finding: No increase in pulm fcn abnormalities 10 years later in GWV

Rationale: Published reports have documented increased prevalence of self-reported respiratory sx among PGWV

Ss: 1036 deployed & 1103 nondeployed PGWV. Not selected by illness status.

Phase III cohort from Natl Health Survey of Gulf War Era Veterans & Their Families -- Kang, Murphy etc

Gave "final list matched DV's & NDVs

Diffs: PGWV ↓age, ↑white, ↑enlisted, ↓education.

Markers: Pulmonary Function

Result: No difference in distribution of PFT results: 64% nl; 16-18% nonreversible awy ds; 10-12% restrictive; 6=7% small airway; 0.9-1.3% reversible airway obstruction.

No diff MD visits for pulm complaints; pulm hospitalizations; # documented episodes asthma, bronchitis, emphysema; pulm meds in last year.

GWV more likely to cite smoking and wheezing.

Interpretation: If more SOB and not worse pulm fcn, consider something else going on. (BUT: tested subgroup not shown to have more SOB)

Karlinsky... Eisen, Kang, Murphy 2004. Late prevalence of respiratory symptoms and pulmonary function abnormalities in Gulf War I veterans. Arch Intern Med 164: 2488-91.

Anthrax - Disability Study

Ss: 716,833 US Army;
includes 154,456 s/p AVA w ≥1 day f/u.
Active duty 12/97-12/01. Exclude if AVA pre1997
Exposure:Rec'd ≥1 dose AVA btn 3/98-2/02
dose; vaccine period; specific lots
Follow-up: 4.25 years total: rates of eval for disability discharge through 2-02.
Analysis: Cox proportional hazards. Person time accruing pre-vaccine is considered "unexposed"
Adjustments: occupation, sociodemographics

Sulsky SI, Grabenstein JD, Delbos RG 2004JOEM 46 (10): 1065-75

Anthrax - Disability Study

Analysis:
Collinearity: check for correl coeff > 0.5, retain member of pair most plausibly associated.
Candidate variables for inclusion: If lead to 15% change in HR (hazard ratio) for vaccine *in any stratum*. Then check for confounding in multivar:
Confounding: 15% change in HR for vaccination felt to ID confounding -- not based on stat signif due to large sample (everything significant)
Assumption: risks constant over the timeframe.

Sulsky 2004 JOEM 46 (10): 1065-75

Anthrax - Disability Study

Additional analysis:
Men vs women
By 1' reason disability: muscskel or neurologic
By disabil eval state: permanent vs temporary
Duty location within SW Asia - to partially mitigate healthy vaccinee effect

Sulsky 2004 JOEM 46 (10): 1065-75

Anthrax - Disability Study

Results: 22% had at least 1 dose (154K/717K)
Higher fraction vaccination in certain groups: special ops; stationed abroad at any time.
89% of those in SW Asia on/after 6-98 and 95% in Korea on/after 1-98 got at least one dose
4% eval'd for disab of whom 15% had rec'd AVA
Unadjusted rate: 1/2 as high for vaccinated 68 vs 140 per 100,000 person months
Unadjusted HR: 0.77 (0.74-0.79): 23% lower likelihood of undergoing disabil eval

Sulsky 2004. JOEM 46 (10): 1065-75

Anthrax - Disability Study

Results: adj for ever stationed abroad during f/u; major command. Vaccinated vs not.

Adj HR all: 0.96 (0.97-0.99)* "benefit"
Adj HR men: 0.96 (0.92-1.00* "benefit"
Adj HR women: 1.04 (.96-1.13)
AVIP period 1: 1.04 (1.00-1.09)* "harm"
AVIP period 2: 0.84 (0.79-0.89)

Sulsky 2004. JOEM 46 (10): 1065-75

Anthrax - Disability Study

Results: adj for ever stationed abroad during f/u; major command. Vaccinated vs not.

1 dose AVA: 1.83 (1.6-2.1)
2 dose AVA: 1.64 (1.43-1.87)
3 dose AVA: 0.91 (0.87-0.94)

Sulsky 2004. JOEM 46 (10): 1065-75

Anthrax Vaccine: Disability