

The Iowa Gulf War Cohort & Case-Control Studies: An Update

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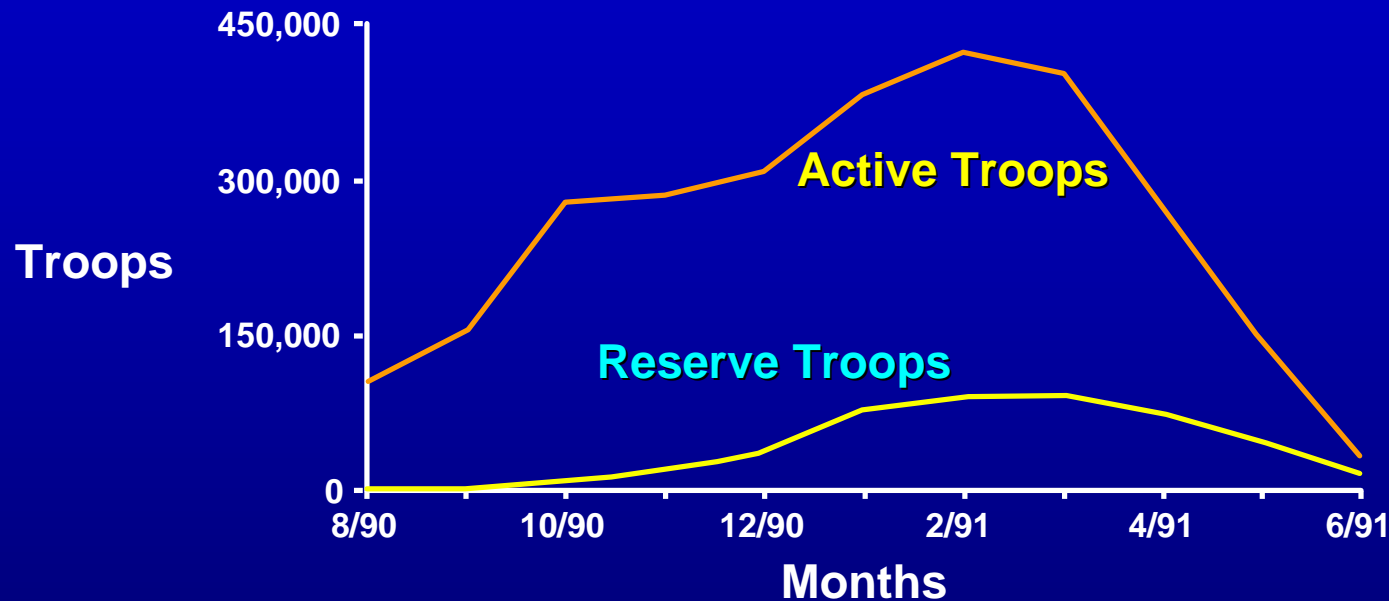
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Timeline of Events

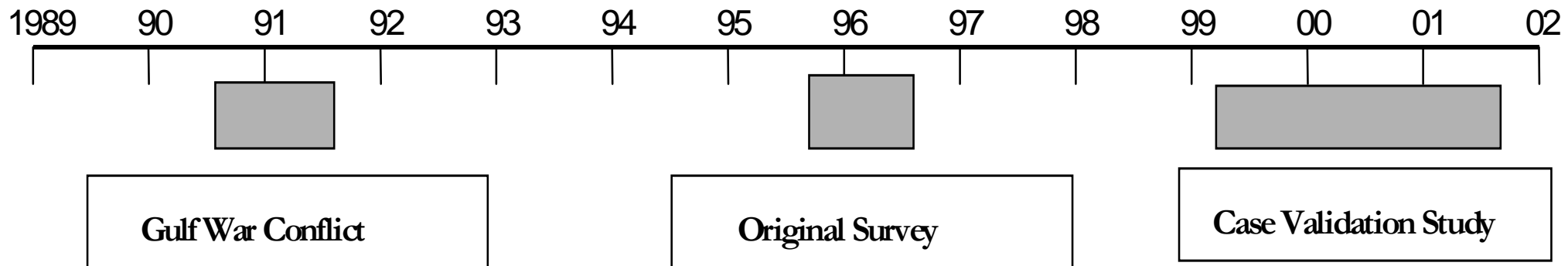
- August 2, 1990: Iraqi forces invade Kuwait
- August 7, 1990: Operation Desert Shield



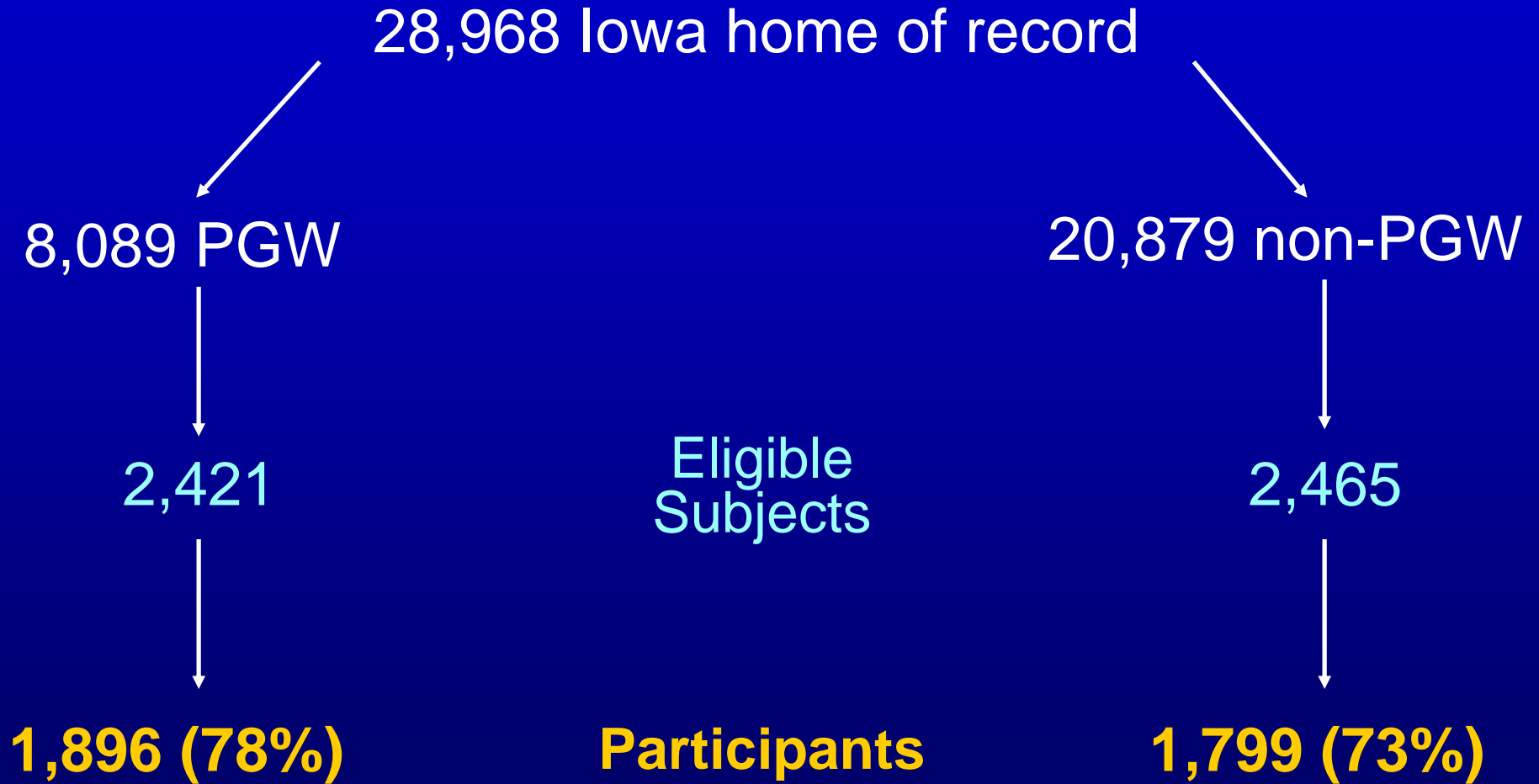
- January 16, 1991: Operation Desert Storm with initiation of air attacks
- January 20, 1991: first oil well fire ignited
- February 24-28, 1991: ground war with restoration of peace
- June 1, 1991: fewer than 50,000 troops
- November 1, 1991: oil well fires extinguished

Iowa Gulf War Research Program

Figure 1. Data Collection Timeline



Iowa Gulf War Cohort



(91% of those for whom a valid phone number was identified)

Iowa Persian Gulf Study: Reported Exposures

	Regular Military	NG/Reserve
Days in Theater	168	139
# Assigned Units	820	137
# Vaccinations (>10)	34%	27%
# Pyridostigmine tabs (>30)	20%	13%
Smoker (current)	34%	33%

Iowa Persian Gulf Study: Reported Exposures

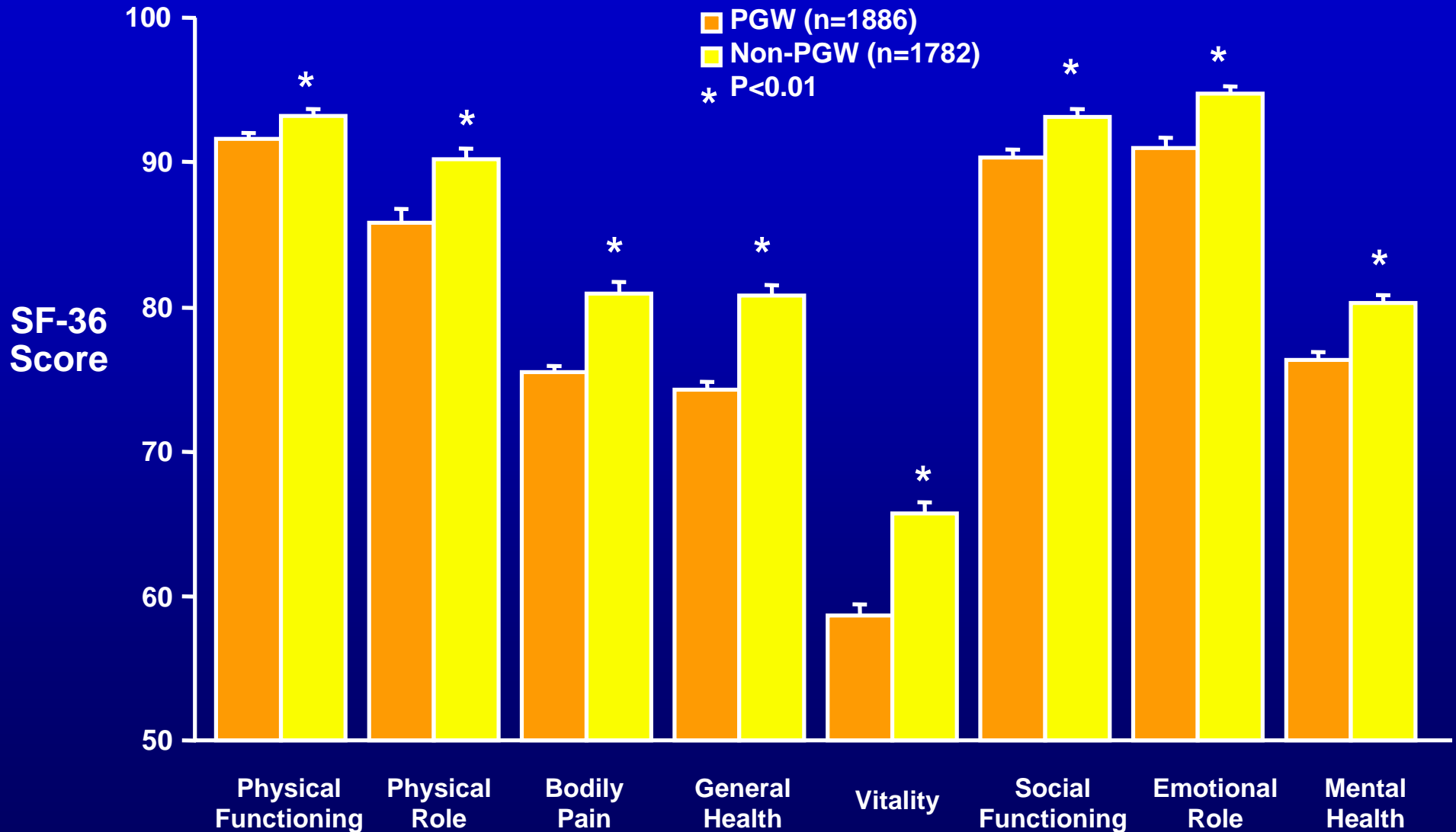
	Regular Military	Nat'l Guard/ Reserve
Solvents/Petrochemicals	89%	91%
Smoke/Combustion products	85%	96%
Infectious agents	84%	93%
Pesticides	44%	63%
Sources of lead	78%	89%
Radiation	27%	16%
Chemical warfare agents	5%	6%
Physical trauma	4%	6%
Psychological stressors	83%	96%

Iowa Persian Gulf Study

Symptoms (a priori outcomes)	Estimated Prevalence		Prevalence Difference (95% CI)	
	PGW (n=1896) %	Non-PGW (n=1799) %		
Cognitive dysfunction	18.7	7.6	10.9	(9.0-12.7)
Fibromyalgia	19.2	9.6	9.3	(7.3-11.2)
Depression	17.0	10.9	6.0	(4.0-7.9)
Anxiety	2.8	1.3	2.7	(1.8-3.7)
Alcohol abuse	17.4	12.6	2.4	(0.4-4.5)
Asthma	7.2	4.1	2.3	(0.7-3.9)
Bronchitis	3.7	2.7	2.3	(1.1-3.4)
Chronic fatigue	1.3	0.3	1.4	(0.9-2.0)
PTSD	1.9	0.8	0.9	(0.3-1.5)

* controlled for age, sex, race, branch of military, and rank

SF-36 Health Related Quality of Life



HRQL in GW & Era Military

- Objective: To examine HRQL of military personnel either deployed, or eligible for, but not deployed to the Gulf War theater.
- The Medical Outcomes Study Short Form-36 (SF-36) was used to assess HRQL.
- Multivariable linear regression identified risk factors for HRQL
--SF-36 physical (PCS), mental component summary (MCS) scores as dependent variables.

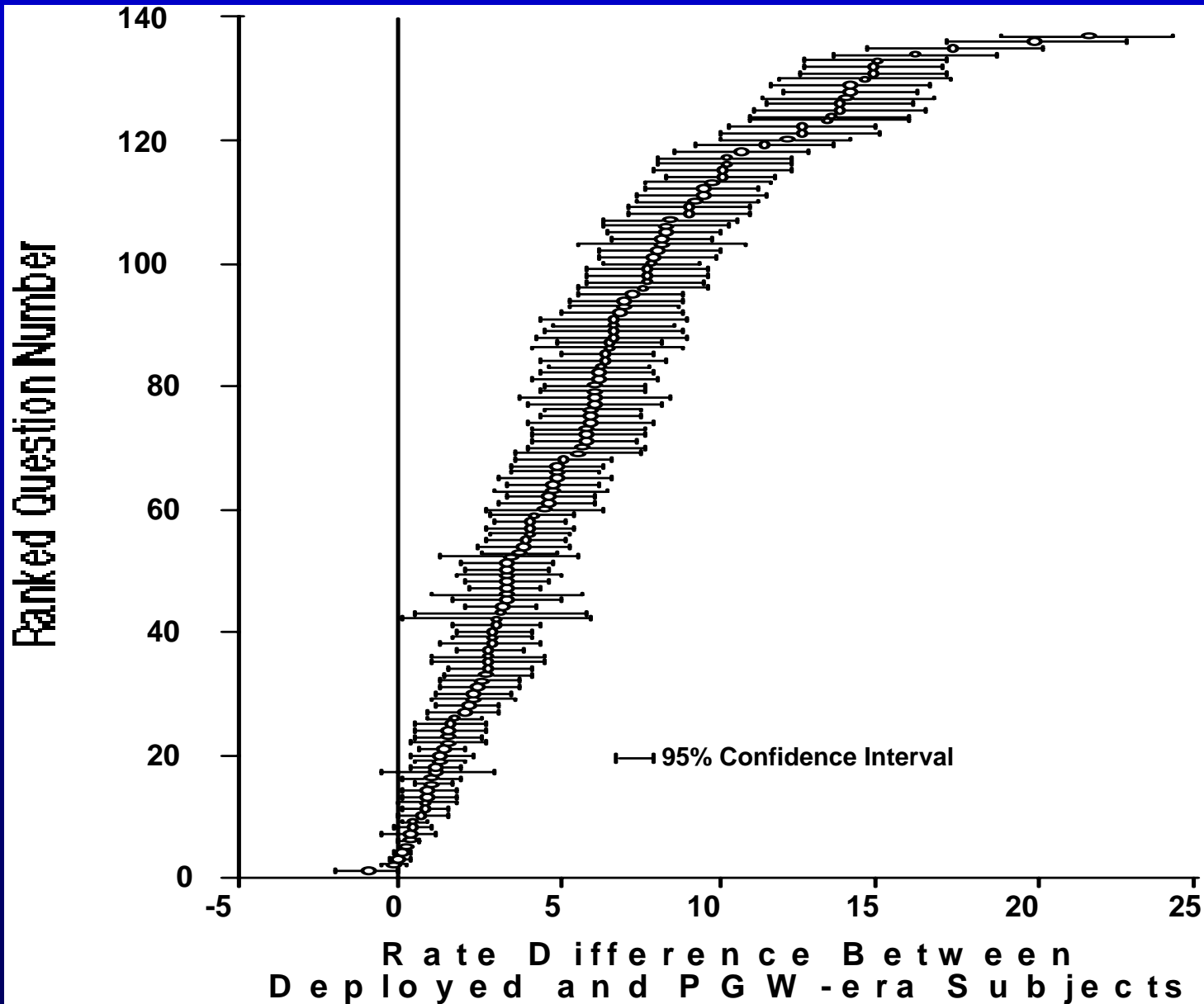
HRQL in GW Era Military: Conclusions

- Deployed slightly poorer HRQL than Non-Deployed, even after adjustment.
- Risk factors for worse HRQL post-deployment:
 - Modifiable factors (*smoking, military preparedness*),
 - Predeployment health (*medical & psychiatric comorbidity*),
 - Social/personality (personality & marital status)*.

Is There a Persian Gulf War Syndrome?

- 50% of deployed, 14% of the nondeployed report current health problems due to military service 8/90 to 7/91.
- Factor analysis identified three replicable symptom factors in the deployed veterans (*convergent correlations ≥ 0.85*).
- Factor score intercorrelations = 0.90 (Somatic Distress), 0.89 (Psychological Distress), and 0.88 (Panic).

Symptom Prevalence Rate Differences (CI_{95}) for Deployed versus Non-deployed Controls



Syndrome Analysis: Conclusions

- Increased prevalence of nearly every symptom assessed from all bodily systems among the GW veterans difficult to explain pathophysiologically as a single condition.
- Same patterns of symptoms among deployed and nondeployed suggests that the health complaints of PGW veterans are similar to those of the general military population, but at higher rates.

Other Population-based Studies (with controls): No Evidence of Unique Syndrome

- Fukuda et al, JAMA, 1998.
- Ismail et al, Br. Med. J., 1999.
- Knoke et al, Am. J. Epidemiol, 2000.

Note importance of validation sample (typically nondeployed)

Exposures to the Kuwait Oil Fires and Association with Asthma and Bronchitis

- Examined relationships between respiratory illness and both self-reported and modeled exposures to oil fire smoke.
- Modeled exposures using GIS to integrate spatial and temporal records of smoke concentrations with troop movements from global positioning systems records.
- 600,000 modeled data points to represent smoke concentrations to a 15 km resolution.
- Outcomes included respiratory symptoms and control outcomes (major depression, injury).

Exposures to the Kuwait Oil Fires and Association with Asthma and Bronchitis

- 94% still in theater during oil well fires and 21% remained in theater over 100 days during fires.
- Modest correlation between self-reported and modeled exposures ($r=0.48$, $p<0.05$).
- Odds ratios for asthma, bronchitis, and major depression increased with increasing self-reported exposure.
- No association between the modeled exposure and any of the outcomes.
- Does not support speculation that exposures to oil fire smoke caused respiratory symptoms among veterans.

Iowa Case-Validation Study

- Objective: estimate of the true magnitude of the health problems encountered by PGW veterans vs. non-PGW veterans
- Focus: Cognitive Dysfunction, Chronic Widespread Pain, Depression
- Design: Case-validation and case-control studies nested within population-based cohort study
- Extensive blinded in-person evaluation, history, family hx, exam, neurocognitive battery, neurologic & neurophysiologic, risk factor, mental health evaluation in GCRC

Iowa Case-Validation Study Sample

- Wave II participants met two criteria:
 - Resided in Iowa or a bordering state at Wave I
 - Eligible participants were either: (1) a “case,” meeting criteria for one or more of the three *a priori*-defined symptom based conditions at Wave I: Cognitive Dysfunction, Chronic Widespread Pain, and Major Depressive Disorder; or (2) a “control,” not meeting criteria for any of these three conditions.
- Sampling parameters
 - PGW and non-PGW veterans sampled ~ 2 to 1 ratio
 - cases and controls sampled ~ 2 to 1 ratio
 - Controls – adaptive randomization (age, sex, branch)
- N = 602

Exercise/Fitness

- Symptomatic cases less often follow a regular program of vigorous physical exercise (adjusted OR=0.6 (CI 95=0.4, 0.9))
- Symptomatic more often self-rate fitness as Somewhat/Extremely unfit (aOR=2.5 (1.6, 4.0))

Evidence of Validity

- Cases have increased Outpatients Visits (>5 in Past Year) (aOR=2.4 (CI95 1.4, 4.2))
- Similar ER (aOR 1.3 (0.9, 1.9) and Inpatient stays (aOR=1.3 (0.7, 2.4))
- Disability rating higher (Blinded Examiner, Slight impairment/ Severely limited/Unable to have paid employment, aOR 2.0 (1.3, 3.1))
- Distress rating higher (Blinded Examiner, Moderate/Severe aOR= 3.3 (1.8, 5.9))

Defining Subjective Cognitive Dysfunction (CD)

Report of \geq of following criteria at Wave I:

- severe memory impairment
- at least “moderately” bothered by confusion or disorientation
- “moderately” bothered by difficulties with 2 or more: thinking clearly, concentrating, comprehending, reading comprehension, slips of the tongue, forgetfulness, or memory problems
- being bothered “quite a bit” by any one of the previously listed symptoms.

Results: Cognitive Dysfunction (CD)

- Subjective CD a/w higher levels of distress, higher rates of depression, and PTSD among both PGW and non-PGW veterans.
- Neurocognitive impairment rates higher among PGW veterans with earlier subjective CD (26%) than PGW veterans without subjective CD (15%).
- PGW and non-PGW veterans had comparable mean neuropsychological performances.
- PGW veterans did not have a higher risk of neurocognitive impairment (OR=1.2, CI95=0.6, 2.1).
- Neurocognitive impairment associated with anxiety disorders and alcohol dependence.

Defining Persistent Chronic Widespread Pain (CWP)

- Chronic Widespread Pain at Wave II
 - Overall body pain
- AND
- Persistent pain or aches in more than 1 joint, OR
 - Persistent problems with muscle tension, aches, soreness, or stiffness four weeks prior to visit

Results:

Chronic Widespread Pain (CWP)

- 37% met *a priori* criteria for CWP at T₁, 30% at T₂
- 18% met criteria for CWP at both T₁ and T₂ (persistent CWP)
- CWP -- important determinant of health care utilization, disability and health-related quality of life in Gulf War veterans.
- Relationship exists between persistence of CWP and disability and illness.
- Veterans with persistent CWP had worst health outcomes.

Modeling: Chronic Widespread Pain

	ODDS RATIO	95% CI
• Officer status	0.44	(0.25-0.77)
• NG/Reserve (active duty)	1.53	(1.27 - 1.85)
• Smoking, Current (never, prior)	1.32	(1.00 - 1.74)
• Combat	3.36	(2.57 - 4.41)
• Seen MH professional (pre-8/90)	1.61	(1.17 -2.23)
• Somatic distress (pre-8/90)	1.60	(1.46 - 1.75)
• Psychological distress (pre-8/90)	0.71	(0.51 - 0.99)

Defining Depression

- *Validated Depression at T₂*
 - Structured Clinical Interview Diagnosis, all mental health data (Best estimate diagnosis) reviewed by psychiatrist
 - Meets SCID criteria for lifetime depressive diagnoses
 - Major Depressive Disorder
 - Chronic Dysthymia
 - Depressive Disorder – NOS

Depression in GW Veterans

- Deployed veterans more likely to meet MDD (PRIME-MD) telephone interview) than non-deployed.
- Deployed veterans comparable lifetime MDD (SCID, best estimate dx) than non-deployed veterans (30% vs. 37%, $p=0.1316$).

Results: Depression

In sub-sample analyses of Depressed veterans (132 PGW, 60 non-PGW)

Depressed PGW veterans more likely to have current PTSD, any anxiety disorder, any psychiatric disorder than Depressed non-PGW veterans

Depressed PGW veterans reported more distress, less positive temperament, more severe PTSD symptoms than Depressed non-PGW veterans

Anxiety Conditions

- Deployed had higher prevalence of anxiety conditions than non-PGW veterans (5.9% vs. 2.8%, OR= 2.1, 95% CI=1.3 to 3.1).
- PTSD, panic disorder, and generalized anxiety disorder at rates nearly twice expected.
- Risk Factors (independent): Prior psychiatric tx, previous dx. of depression, anxiety, or a medical disorder.
- Elevated risk (independent): Regular military (versus Guard/Reserve), enlisted (versus officer), cigarette smoking, low level of military preparedness, incarceration, and antisocial traits.

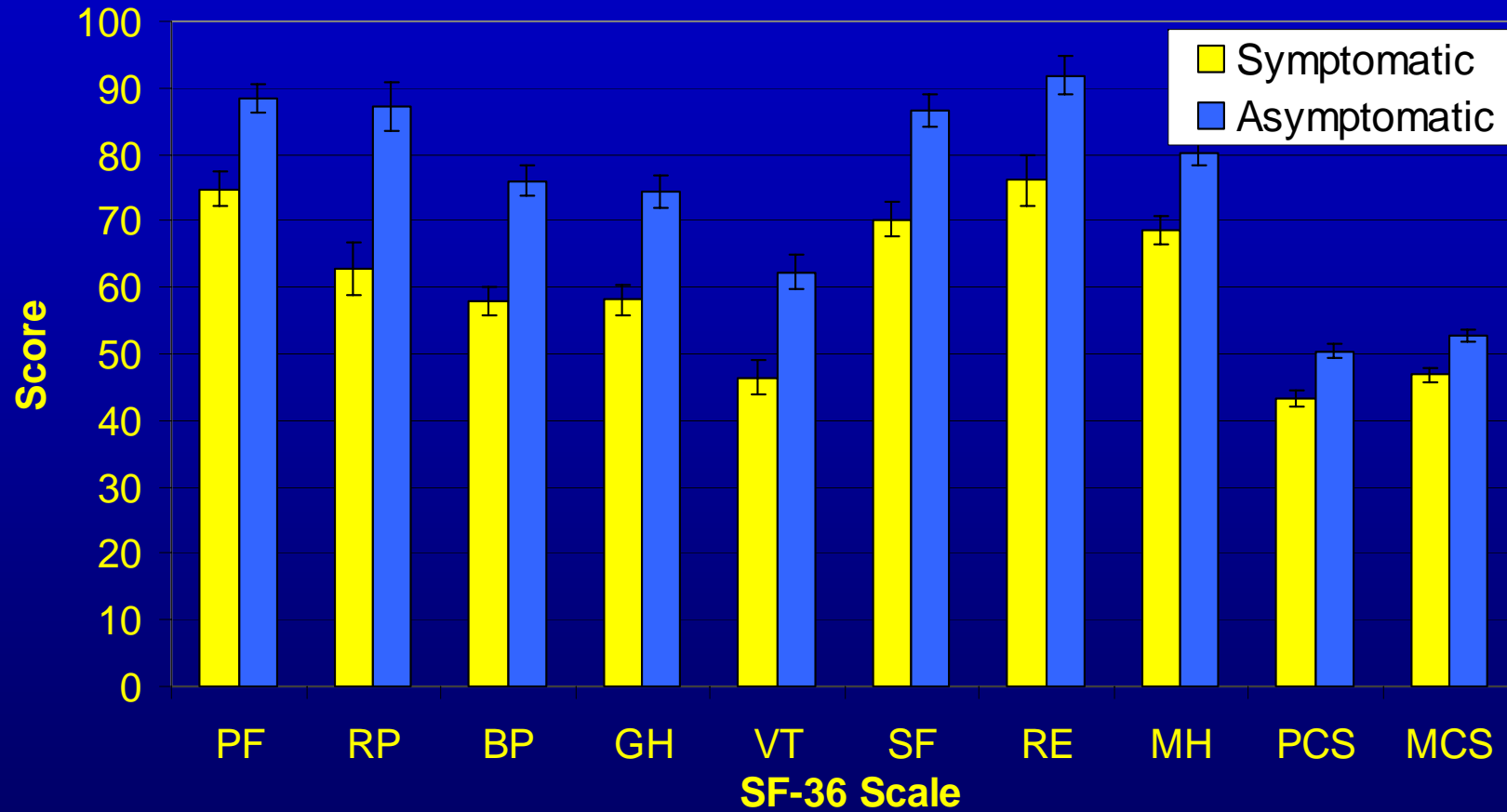
Mental health comorbidity

- Mental health disorders defined with SCID-IV (Wave 2).
- Health Utilities Index Mark 3 (HUI3) to measure health-related quality of life (HRQoL).
- More than 11% (n=69) had coexisting current mental disorders spanning two or more categories.
- Mental disorder comorbidity had lower HUI scores than veterans with ≤ 1 mental disorders (mean 0.41 ± 0.30 vs. 0.72 ± 0.25 , $p < 0.0001$).
- Co-occurrence of mental disorders that span at least two mental disorder categories a/w impaired HRQoL.
- Early identification of mental health comorbidity may lead to interventions.

Hypochondriasis

- 10% of Wave 2 sample met criteria for hypochondriasis.
- 40 met criteria in cases (aOR 14.3 CI95=3.4, 60.1)
- Risk factors include physical conditions, negative temperament, lack of social support, and perceived stress.

Health Related Quality of Life of Veterans assessed in the Case Validation Study



Other important findings

- Symptomatic status significantly a/w greater prevalence of Lifetime Major Depressive Disorder (aOR=4.2 [2.6, 6.7]) and Chronic Widespread Pain (aOR= 5.2 [3.3, 8.1])
- Symptomatic status not associated with objective Cognitive Dysfunction (aOR=1.7 [1.0, 3.0]).
- Symptomatic status at increased risk for
 - Any Mood Disorder – Lifetime (aOR 3.3 (2.2, 4.9))
 - Any Somatoform Disorder – (aOR 4.2 (1.1, 15.7))
 - Any Substance Abuse Disorder – (aOR 1.7 (1.2, 2.4))
 - Any Anxiety Disorder – (aOR 3.4 (2.2, 5.2))

Summary

- Population-based cohorts show increased symptomatology, increased multisymptom illness, impaired HRQOL in deployed
- No evidence of unique syndrome when appropriate controls (non-deployed) and appropriate methods
- Increased validated outcomes of chronic widespread pain, depression, anxiety
- Subjective cognitive dysfunction c/w anxiety, alcohol, depression
- Symptomatic individuals have impaired HRQOL, increased outpatient utilization
- Predeployment factors consistently related to postdeployment illness: predeployment physical and mental health, readiness, personality, social factors, lifestyle (smoking, alcohol, exercise)

Conclusions

- Gulf war illness, not Gulf War syndrome
- Individuals with illness attributed to deployment need acknowledgement of problem, careful medical and mental health care
- Need to collect predeployment risk factors
- Consider not deploying, more extensive training, carefully monitoring, or reassigning those at greatest risk
- Failure to consider mental health outcomes as one of multiple explanations for some individuals not supported by extensive evidence
- Focus on prevention, early identification, early treatment
- Research needed on vulnerability factors, prevention, identification & treatment of multisymptom illness, mental health, improving tx. guidelines, improving quality of care