Presentation 12 – Beatrice Golomb

Gulf War Research Update: October 2004

Beatrice Golomb, MD, PhD

Topics

- Epidemiology
- Health Effects
- Mechanisms: AChEi
- Related Conditions

Epidemiology

Male UK GWV Self-reported health

SUMMARY:

- 24% "extra" of male GWV have health problems, over nondeployed
- Symptoms fit the profiles we are by now familiar with

Simmons, Maconochie, Doyle 2004. Self-reported ill health in male UK GWV: retrospective cohort study. BMC Public Health 4:27

Male UK GWV Self-reported health

Goal: Assess subjective health state in UK GWV vs nondeployed. Seek to avert selection bias by asking all

Intended Ss: Sent to all UK GWV + comparison cohort stratum-matched on sex, age (5-yrs), service, rank, serving status at time of Gulf (regular, reservist), fitness to be deployed (Army/AirForce only).

Sent to about 51,600 of each.

Actual Ss: 42,818 responded = 48%.

Maconochie birth outcomes cohort

Response rate not broken down by Gulf vs not.

Primary outcome: reporting ≥1 new medical problem or change in general health since 1990. 36 ICD-10 categories

Simmons, Maconochie, Doyle 2004. Self-reported ill health in male UK

Male UK GWV: self-reported health

	GWV□	NGWV	Dif
≥1 new symptom since 1990	61%	37%	24%

***Among those GWV reporting symptoms*:**
Median 2 among GWV vs 1 among NGWV

Simmons, Maconochie, Doyle 2004. Self-reported ill health in male UK GWV: retrospective cohort study. BMC Public Health 4:27

Male UK GWV: self-reported ill health

Most common reported symptoms	by GWV	by NGWV
Musculoskeletal	15%	
"Other" symptoms	13%	
General fatigue	11%	
Memory/Concentration	7.9%	
Skin allergies	7.6	
Accidental injury*		2.6%

*Cited as "among" the most common sx in NGWV

Simmons, Maconochie, Doyle 2004. Self-reported ill health in male UK GWV: retrospective cohort study. BMC Public Health 4:27

Male UK GWV, cont'd

Over 85% of sx more common in GWV vs not

Some of top risk ratios	%GWV	%ctrl	Adj OR*
General fatigue	10.8	1.2	9.6 (8.3-11.1)***
Memory/Concentration	7.9	0.4	19.6 (15.5-25)***
Mood swing/aggression/irritabil	7.3	0.4	20.9 (16.2-27)***
Muscle pain/weakness	2.0	0.4	4.5 (3.5-5.7)***
Night sweats	1.4	0.1	9.9 (6.5-15.2)***
General decline in fitness/health	1.2	0.3	4.4 (3.2-6.0)***
Respiratory problems NOS	3.8	1.2	3.3 (2.9-3.9)***
Weight gain/loss	2.2	0.6	3.4 (2.7-4.1)***

*Adjustment for age at survey, service & rank at time of Gulf, serving status at time of survey, alcohol, smoking

Simmons, Maconochie, Doyle 2004. Self-reported ill health in ale UK GWV: retrospective cohort study. BMC Public Health 4:27

Illness Beliefs vs Symptoms

Conclusion: Illness beliefs significantly predict health outcomes after controlling for demographic and mental health variables.

"Gulf War veterans beliefs may impact clinical outcomes. Discussing illness beliefs and providing accurate information is an important component of medical care for Gulf War veterans.

Problem: Shows beliefs are associated with health outcomes

States beliefs "impact" outcomes; infers causality

But health outcomes *should* influence "beliefs" (views) about health

"Beliefs" affected by health, e.g.: My symptoms are staying the same; are getting worse; are disabling; often come back.

Hunt, Richardson, Engel, Atkins, McFall Aug 2004. J Occup Environ Med. Gulf War veterns' illnesses: A pilot study of the relationship of illness beliefs to symptoms severity and functional health status.

Illness Beliefs vs Symptoms

Ss: 583 GWV: 296 VA Seattle s/p "comprehensive" registry evaluation; or 296 Walter Reed current active or reserve seeking care from Gulf War Health Center.

Date: Evaluations between 3-98 to 11-01

Measures:

- VIBS = Veterans Illness Belief Survey: 29 Qs about belief about etiolog, clin. course & proper treatment of sx & illness
- PTSD-Checklist - Military version (PCL-M)
- PHQ Somatic Symptom Checklist: 20sx using modified version of somatoform symptom assessment module of PHQ (Physician Health Questionnaire)
- Prime MD PHQ: Self-report version; assess for mental d/o's
- SF-36: Assesses functional status/ quality of life

Hunt, Richardson, Engel, Atkins, McFall Aug 2004. J Occup Environ Med. Gulf War veterns' illnesses: A pilot study of the relationship of illness beliefs to symptoms severity and functional health status.

Illness Beliefs vs Symptoms

Outcomes:

- SF-36 MCS
- SF-36 PCS
- Symptom checklist

Analysis:

Regression to determine impact of beliefs about illness on outcomes

3 Models:

- Demographic
- Demographic + Mental disorder variables
- Demographic + mental + Beliefs

Hunt, Richardson, Engel, Atkins, McFall Aug 2004. J Occup Environ Med. Gulf War veterns' illnesses: A pilot study of the relationship of illness beliefs to symptoms severity and functional health status.

Illness Beliefs vs Symptoms

After adjusting for demographic variables and mental disorders:

Illness beliefs explained outcomes

- 23% of variance in physical symptom severity (SSC) score
- 33% of variance in PCS score
- 5% of variance in MCS score

Comment: Just because you put a variable on the RHS of an equation, and it is significantly related to the variable you put on the LHS, does not mean it is "causing" the factor you put on the LHS of the equation!

*Try to publish same study in recognized conditions like ALS!

Hunt, Richardson, Engel, Atkins, McFall Aug 2004. J Occup Environ Med. Gulf War veterns' illnesses: A pilot study of the relationship of illness beliefs to symptoms severity and functional health status.

Nisenbaum: Factor Analysis

Ss: 3454 UK GWV; 1979 Bosnia deployed; 2577 GW era; 1163 US GWV from 4 AirForce Units

Outcomes: Surveyed 1995 for health/symptoms

Design: Split halves Factor Analysis (in each sample): Exploratory & confirmatory. Promax oblique rotation.

Result:

- 4 correlated factors in each sample: Resp; mood-cog; peripheral nervous; GI/urogenital

GI/urogenital factor in UK Gulf different from GI factor in Bosnia and Era.

UK sim to US GW for GI, resp, mood-cog: despite differences in sx inventories. Musculoskeletal factor only elicited from US PGW sample.

Nisenbaum R. 2004. Population Health Metrics 2:8

Nisenbaum: Factor Analysis

Notes similar illnesses in those who did not participate in Gulf War "(albeit at lower rates and with different specific characteristics)"

" so we believe that this pattern of symptoms is not unique to Gulf War service nor does it represent a unique illness or 'Gulf War syndrome'"

- Cites similarities to other war syndromes e.g. Civil War and Boer War

- Predicts similar from Afghanistan and Iraq

Nisenbaum R. 2004. Population Health Metrics 2:8

Specific Health Effects

Infertility in Male UK GWV

Ss: Same as previous Maconochie sample. 42818 completed questionnaires = 53% GWV, 42% NGWV (total 48%)

Design: retrospective cohort (mailed survey)

Primary outcome: a. Failure to achieve conception (type I infertility) or live birth (type II infertility) after the Gulf with trying at least a year and consulting a doctor.

b. Time to conceive for pregnancies fathered by men not reporting fertility problems

Maconochie, Doyle, Carson 1004. BMJ, doi:10.1136/bmj.38163.620972.A

Infertility in Male UK GWV

	%GWV	%NGWV	OR
Fertility prob (consulted doctor)	7	5	1.38 (1.2-1.6)
• Type I	2.5	1.7	1.41 (1.1-1.9)
• Type II	3.4	2.3	1.50 (1.2-1.9)
Prolonged time to conception if achieved:			
• Time >1 year	9.1	7.8	1.18 (1.04-1.3)

Time trying unsuccessfully for a child: No diff

Time first tried till consulted doctor: No diff

□Maconochie, Doyle, Carson 1004. BMJ, doi:10.1136/bmj.38163.620972.A

Infertility in Male UK GWV

•Suggestion of ↑:	GWV	NGWV	OR
•Teratospermia	% (N)	% (N)	
Type I	.2 (21)	.1 (6)	2.02 (.79-5.14)
Type II	.3 (26)	.1 (6)	2.55 (1.03-6.3)
•Oligasthenoteratospermia			
Type I	0.1 (8)	.03 (2)	2.17 (.43-10.9)
Type II	0.1 (9)	.03 (2)	2.47 (.51-12.0)

Adjusted for rank *□& serviice in GW; age of both participant & female partner at 1st consult for infertility; or in fertile, first pot-gulf conception

Maconochie, Doyle, Carson 1004. BMJ, doi:10.1136/bmj.38163.620972.A

Infertility in Male UK GWV

Consistent with Australian study: GWV had 40% ↑ in fertility problems

Conflict with Danish study: no evidence of effect of Gulf War service on markers of male infertility

Adjusted for rank *□& serviice in GW; age of both participant & female partner at 1st consult for infertility; or in fertile, first pot-gulf conception

Maconochie, Doyle, Carson 1004. BMJ, doi:10.1136/bmj.38163.620972.A

Health Effects - Objective Markers

Quantitative Balance Tests

Summary:

Quantitative balance testing abnormalities are more common in GWV than in CFS; and more common in CFS than in in healthy controls.

Quigley, Maney, Natelson, Findley. Arch Phys Med Rehabil 2004, Sep 85(9):E34. Poster abstract. Quantitative balance and self-reported health status in medically unexplained illness.

Quantitative Balance Tests

Ss:

- 19 GWV with "medically unexplained illness"
- 27 CFS
- 17 age-matched controls

Equitest SOT (sensory Organization Test):

6 conditions on movable platform:

Eyes closed/quiet. Sway visual. Sway support. Sway support eyes closed. Sway support&visual.

Quigley, Maney, Natelson, Findley. Arch Phys Med Rehabil 2004, Sep 85(9):E34. Poster abstract. Quantitative balance and self-reported health

Quantitative Balance Tests

scoring >2SD below normal

- GWV 50%
- CFS 35%
- Normal 10% $p < 0.001$

"Quantitative balance testing is abnl in many deployed veterans with medically unexplained illness". High correlation with self-reported health "suggests that subtle balance problems are important factors in perceived health status" (No -- correlate with health!)

Quigley, Maney, Natelson, Findley. Arch Phys Med Rehabil 2004, Sep 85(9):E34. Poster abstract. Quantitative balance and self-reported health

Heart Rate Variability (HRV)

Summary: Big differences in autonomic function by HRV among GWV & FM vs controls -- more pronounced for GWV

- Short-term HRV differences are apparent for men and women
- Intermediate- & long-term HRV differences are apparent only in women
- Magnitude of difference nontrivial; e.g. like post-MI patients for some indices, worse than post-MI for others.

Stein..., Clauw Oct 2004. Arthritis and Rheumatism 51(5):700-8. Sex Effects on Heart Rate Variability in Fibromyalgia and Gulf War Illness

Heart Rate Variability

Ss:	Male	Female	Total
• GWV	6	5	11
• FM	7	19	26
• Controls	18	18	36

Measure: HRV from 24h Holter.
Daytime; Nighttime; and 24h HRV

Stein..., Clauw Oct 2004. Arthritis and Rheumatism 51(5):700-8. Sex Effects on Heart Rate Variability in Fibromyalgia and Gulf War Illness

Heart Rate Variability (HRV)

Ss	GWV	FM	Ctrl	p
Longer term HRV				
HR	76	74	70	.065
SD NN, longterm	117	125	140	.05
Ln ULF	9.2	9.2	9.4	.1
Intermediate term HRV				
Ave SD over 5min	53	63	68	.056
Ln VLF power	7.2	7.5	7.6	.054
Ln LF power	6.4	6.9	7.0	.050
Short term HRV				
%NN>50msec dif prior	6.7	12.6	17.5	.023
RMS difs NN	27	37	43	.036
Ln HF power	5.2	5.9	6.1	.044

HR = hrt rate; SD = stdd dev; ULF = ultra low freq; NN = normal-to-normal

Heart Rate Variability (HRV)

	GWI		Ctrl	
Longterm HRV	F	M	F	M
SD NN	97	138*†	138	142
Ln Ultra LF	8.8	9.6*†	9.4	9.6
Intermediate HRV				
SD, 5min	41	64*†	69	67
Ln Very LF	6.7	7.7*†	7.7	7.6
Ln LF	5.8	7.0*†	7.0	7.0
Shortterm HRV				
%NN>50ms	3.8	9.8†	19.5	15.5
RMS SD	22	33†	45	41
Ln HF	4.9	5.7†	6.2	5.9

*male signif different from female; †GW signif diff from ctrl
SD = std dev; NN = beat-to-beat interval; Ln = log(e);

Heart Rate Variability (HRV)

Day-Night differences similar to controls

	GW		FM	
Long	F	M	F	M
SD NN, day	89	109	133	117
SD NN, night	71	102	93	106
Intermediate				
SD, 5 min, day	42	57	69	63
SD, 5 min, night	40	73	67	74
LN LF, day	5.9	6.8	7.0	6.4
LN LF, night	5.6	7.2	6.9	7.2
Short term				
%NN>50ms, day	2.7	5.7	17.2	12.3
%NN>50ms, night	6.0	20	24	23

Depression in GWV

Summary, theirs:
There is no difference between depression in GWV vs in Era

Summary, mine:
There is a difference between depression in GWV vs in Era

Black et al 2004. Ann Clin Psychiatry 16: 53-61. Depression in veterans of the first Gulf War and comparable military controls.

Depression in GWV

	GWV	Era	
No ↑ lifetime depression:	**30.3%**	**36.6%**	**NS**

Among those with depression:

- **No ↑ somatoform d/o** **1.06 (NS)**
- **No ↑ hypochondriasis** **1.1 (NS)**
- **- ↑ Cognitive dysfunction** **2.3 (1.2-4.3)**
- **- ↑ Severe pain/distress** **2.5 (1.04-6.1)**
- **- ↑ Severe disability (not quite significant)**
- **- ↑ PTSD** **4.0 (2.0-6.0)**
- **- ↑ Anxiety disorder** **3.2 (1.6-6.3)**

Black et al 2004. Ann Clin Psychiatry 16: 53-61. Depression in veterans of the first Gulf War and comparable military controls.

Depression in GWV

Subjects:

Wave I (prior): 3695 (76% participation) Iowa veterans (GWV or EraV), stratified by age, gender, race, branch of military, enlisted vs officer.

Wave II (current): 602 Ss interviewed.

Selected for having, during Wave I evaluation:

Depression OR **cognitive dysfcn** OR **widespread pain**: any one, any two, all three, or control (8 strata)

Then stratified GWV vs Era

Among Depressed:

Current	%GWV	%Era	RR (95%CI)
	n=132	*n=60*	
MDD	30.3	23.2	1.43 (.7-2.9)
Any mood d/o	50.8	36.7	1.78 (.95-.3.3)
Anxiety d/o,any	51.5	25	3.2 (1.6-6.3)
PTSD	27	5.0	7.1 (2.1-24.2)
Specific phobia	11.4	0	7.1 (2.1-24.2)
Somatoform d/o	**5.3**	**5.0**	**1.06 NS**
Alcohol abuse	10.6	5.0	2.3 NS(.7-6.8)

Black et al 2004. Ann Clin Psychiatry 16: 53-61. Depression in veterans of the first Gulf War and comparable military controls.

Oil Fires & Resp Health

Summary:

GWV more resp sx s/o asthma

- More asthma & bronchitis dx'd since war
- No worse lung fcn

Oil fire exposure assoc decr FVC

Dust storm exposure assoc impr peak flow

Kelsall et al 2004. Thorax 59: 897-903.

Oil Fires & Resp Health

Ss: 1456 of all 1871 Australian GWV + 1588 of sampled 2924 era controls frequency matched by sex, service type, 3-yr age bands, officer/non w/o Army; aircrew/non w/in Air Force.

Date of study: Aug 2000-Apr 2002

Assessment: PE: wheeze, pharyngitis, RR

•Hx asthma; bronchitis; emphysema

•Ventilatory dysfcn

Kelsall et al 2004. Thorax 59: 897-903.

Oil Fires & Resp Health

Asthma: doctor dx; or being woken by an attack of SOB in past 12 mo; asthma med

Bronchitis: doctor dx; or cough >3mox≥2yr & FEV1/FVC < 70%

Emphysema: sob hurrying on level; w/ slight hill; walking w/ others your age; stop for breath walking at your own pace; OR FEV1/FVC < 70%

Ventilatory fcn: Normal; obstructive; restrictive; mixed

Oil Fires & Resp Health

Respiratory Sx	GWV	Era	OR*	95%CI
Wheeze only	45	19	1.4	1.2-1.7
Wheeze w/o old	17	11	1.6	1.3-2.0
Wheeze+breathless	12	7	1.8	1.3-2.3
Nocturnal chest tight	14	10	1.4	1.1-1.9
Nocturnal cough	24	18	1.4	1.1-1.7
AM cough	10	8.8	1.2	0.9-1.5
Spont dyspnea	8	5	1.6	1.1-2.2
Post-exertion sob	22	17	1.3	1.1-1.6
Nocturnal SOB	5.6	3.7	1.5	1.0-2.2

*adjusted for age, ht, wt, smoking, atopy, education, marital, service, rank

Oil Fires & Resp Health

Respiratory Sx	GWV	Era	OR*	95%CI
Wheeze on auscultation	1.6%	0.6%	2.6	1.1-5.9

Other PE findings: most abnormalities slightly more common for GWV (data not given); but significant only for the above

Kelsall et al 2004. Thorax 59: 897-903.

Oil Fires & Resp Health

Respiratory Dx	GWV	Era	OR*	95%CI
Asthma, Dr. Dx	12.0	10.3	1.2**	NS
Asthma, use of meds	4.3	3.2	1.4	NS
Asthma, ECRHS defn	10.2	7.5	1.4	1.1-1.9
Airflow ltn: FEV1/FVC<70	6.4	8.4	0.8	NS
Emphysema, wkg defn	11.1	11.0	1.0	NS
Bronchitis, Dr dx p 1990	47	27	1.9**	1.2-3.1

*adjusted for age, ht, wt, smoking, atopy, education, marital, service, rank

**adj for age, education, marital, service, rank

Kelsall et al 2004. Thorax 59: 897-903.

Oil Fires & Resp Health

Relation of oil fires and dust storms to ECRHS asthma

SMOIL,	%asthma		
none	9%		
any	11%	1.2	NS
low	12%	1.3	NS
high	9%	0.9	NS
Dust storms			
no	9%		
yes	12%	1.3	NS
Deployment completed before air war			
yes	7%		
no	11%	1.7	1.0-2.9

Oil Fires & Resp Health

Relation of oil fires and dust storms to other

	FEV1	FVC
SmOIL*	NS	dose-resp**
Dust storm*	NS	NS
Deployed b4 war	NS	NS

*Tests: any, low, high, dose resp

**$p < 0.05$

Kelsall et al 2004. Thorax 59: 897-903.

Mechanisms: AChEi

Low Level Sarin in Rats

Ss: Male albino SPF rats 180-200g, groups of 10

Exposure: Low Level Sarin x60 min inhaled:

- Level 1: AChEi <20%; no clin signs "or sx"*
- Level 2: AChEi 20-30%; no clin signs or sx
  - Level 2S: single exposure
  - Level 2R: repeat exposure: 3x (every other d)
- Level 3: AChEi 40-50% & mild clin signs: salivation & miosis (pupil constriction)

*Observe animals for salivation; miosis; tonic-clonic immediately after exposure

Kassa et al. Inhalational Toxicology 16:517-30

Sarin in Rats: Outcomes

Outcomes @ 3 mo after exposure:

- Stress markers: corticosteroids; tyrosine aminotransferase
- Biochemistry:lipid,pr,alb,glc,LFTs,minerals?lytes
- Cholinesterase levels
- DNA & pr- metabolism in liver
- Sarin-induced neurotoxicity using FOB
  = Functional Observational Battery
  = 39 msrs of sensory, motor, & autonomic fcn
- NS excitability w/ convulsive dose of PTZ*

*Pentamethylenetetrazole

Kassa et al. Inhalational Toxicology 16:517-30

Sarin: chemical outcomes

Outcomes **@ 3 mo after exposure:**

- Corticosteroids: ↑ p level 3;
- Tyrosine aminotransferase: monotonic ↑;
  - –Significant after sarin @ level 2S, 2R,3
- Biochemistry: No change
- Cholinesterase levels: No change
- Signif ↓ DNA synth (labeled thymidine incorp):
  - – Significant at level 1, 2S, 3
  - –(but no change amount DNA or protein)

Kassa et al. Inhalational Toxicology 16:517-30

Sarin: Clinical outcomes

• Sarin-induced neurotoxicity using FOB

Sarin Level:	Ctrl	I	2S	2R	3
Gait d/o	1.0	1.0	1.0	2.0***	2.0***
Gait Score	1.0	1.5	0.3	0.8	2.0**
Mobility	1.0	1.5	0.2	-2.0**	-2.0**
Activity	1.0	1.5	0.3	1.2	-2.0**
Stereotypy	1.0	0.5	2.0	6.0***	4.0**

NS excitability: Incr big & small sz after PTZ, level 2R ($p<.05$)

Kassa et al. Inhalational Toxicology 16:517-30

Sarin: Clinical outcomes

Spatial discrimination:

Little effect with level 2, single exposure

Much bigger effect & more lasting with level 2, repeated

Mostly normalized by 5 weeks but possible residual effect -- assess with larger sample

Kassa et al. Inhalational Toxicology 16:517-30

Mechanisms: ACE

Mechanisms: ACE

Summary:

• GWV with CFS are FAR LESS LIKELY to have any I allele of the ACE gene than healthy GWV.

• However nonveterans with CFS are NOT LESS LIKELY to have any I allele of the ACE gene than healthy nonveterans.

Mechanisms: ACE

Ss:

- 49 GWV/ 61 nonveterans with CFS
- 30 GWV/ 45 nonveteran healthy controls

Assess Genotypes of ACE

Rationale: ACE gene associated with muscle performance; and higher serum ACE activity in CFS than controls

Note: ACEi: used to improve heart muscle fcn

Outcome: Genomic DNA from blood

Vladutiu 2004. Muscle Nerve 30: 38-43

Mechanisms: ACE

No significant differences for alleles or genotypes for some tested genes:

AMPD1

CPT2

Vladutiu 2004. Muscle Nerve 30: 38-43

Mechanisms: ACE

	GWV		Nonvets	
	ICF/CFS	Healthy	CFS	Healthy
ACE allele	n=72	n=46	n=158	n=88
I allele	.15	.48	.45	.50
D allele	.85	.52	.55	.50
	p < 0.0001			
ACE genotype	n=32	n=23	n=59	n=44
II	.08	.35	.22	.27
ID	.14	.26	.46	.46
DD	.78	.39	.32	.27
	p = 0.009			

Mechanisms: ACE

Something different is contributing to CFS in ill GWV relative to controls

GWV with CFS are far less likely to have the I allele, an allele that is associated with endurance and physical performance in elite athletes, army recruits, and other settings; while civilians with CFS are not less likely

Gulf war CFS really is different in a marker that suggests a different vulnerability is involved; in turn suggesting a difference in causative exposures and pathogenesis.

Vladutiu 2004. Muscle Nerve 30: 38-43

Mechanisms: ACE

Something different is contributing to CFS in ill GWV relative to controls.

"We showed a relationship between stress and CFS-like illness in Gulf war veterans. Such a relationship may not exist in nonveteran CFS patients.

Vladutiu 2004. Muscle Nerve 30: 38-43

Related Conditions

Genetic profiles in MCS

Result: MCS cases more likely to have certain variants in enzymes that metabolize toxins

- "CYP2D6 homozygous active" OR 3.36, p = 0.01
- "NAT2 rapid-acetylator" OR 4.14, p = 0.01
- PON1-55 heterozygous OR 2.05, p = 0.04
- PON1-192 heterozygous OR 1.57, p =0.04

Genetic profiles in MCS

Ss: 203 MCS patients; 162 controls from larger case-control study based on "reproducible & validated case definition". U Toronto Hlth Survey

Outcomes: Common polymorphisms in CYP2D6; NAT1; NAT2; PON1; PON2

Genetic profiles in MCS

Result: MCS cases more likely to have:

- "CYP2D6 homozygous active" OR 3.36, p = 0.01
- "NAT2 rapid-acetylator" OR 4.14, p = 0.01
- PON1-55 heterozygous OR 2.05, p = 0.04
- PON1-192 heterozygous OR 1.57, p = 0.04

Genetic profiles in MCS

- CYP2D6 Distribution of genotypes p = 0.02
- NAT2 distribution of genotypes p = 0.03

Theorize:

- CYP2D6 rapid acetylator: create toxic metabolites or affect endogenous chemicals that protect/heighten risk
- NAT2 rapid acetylator: bioactivates arylamines to protein-binding metabolites

McKeown-Eyssen et al Jul 2004 Intl J Epi 33: 971-78. Case-control study of genotypes in multiple chemical sensitivity: CYP2D6, NAT1, NAT2, PON1, PON2, MTHFR.