

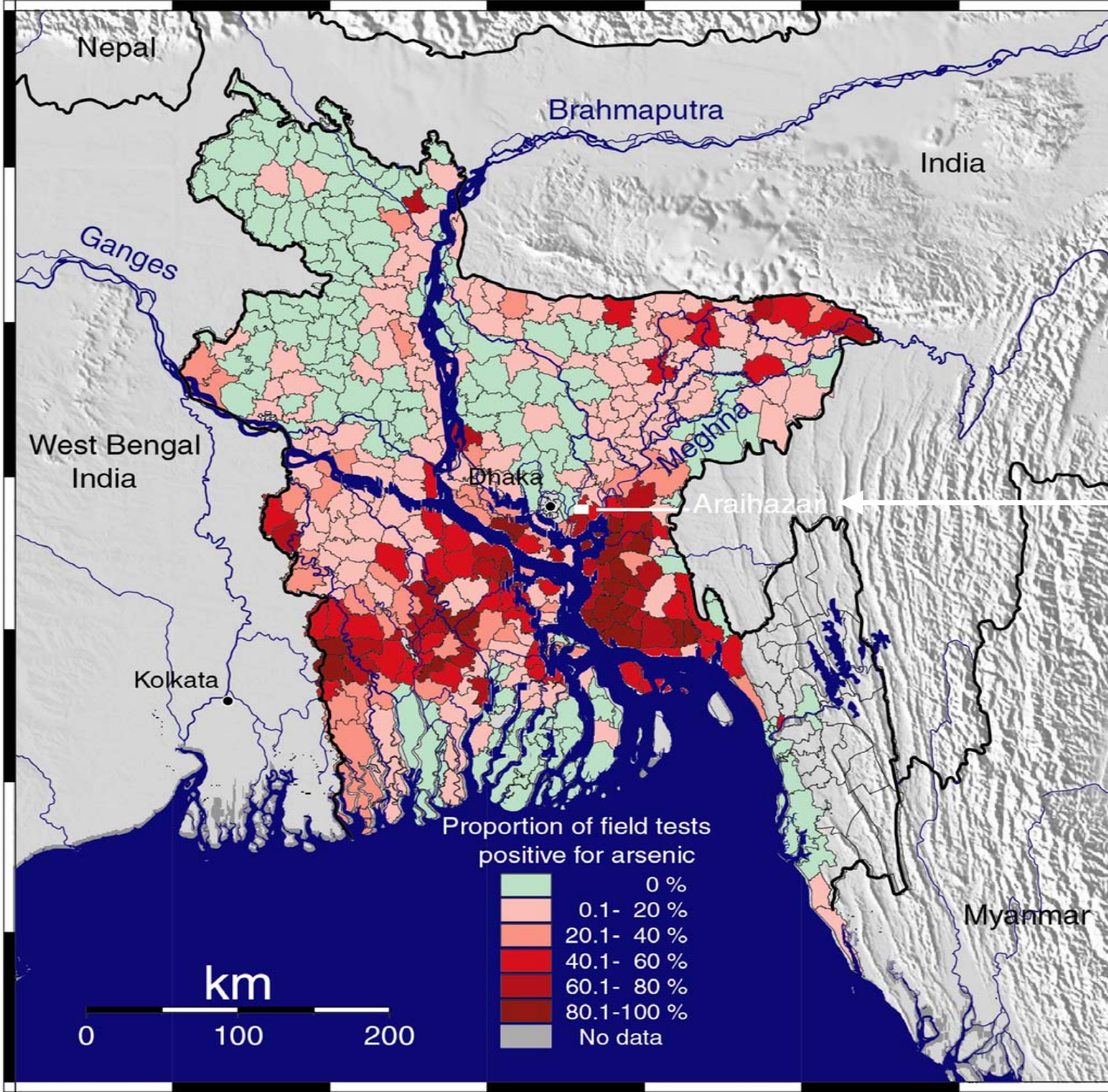


Columbia University
MAILMAN SCHOOL
OF PUBLIC HEALTH

Molecular Epidemiology and Prevention of Health Effects of Arsenic: A Multidisciplinary Approach

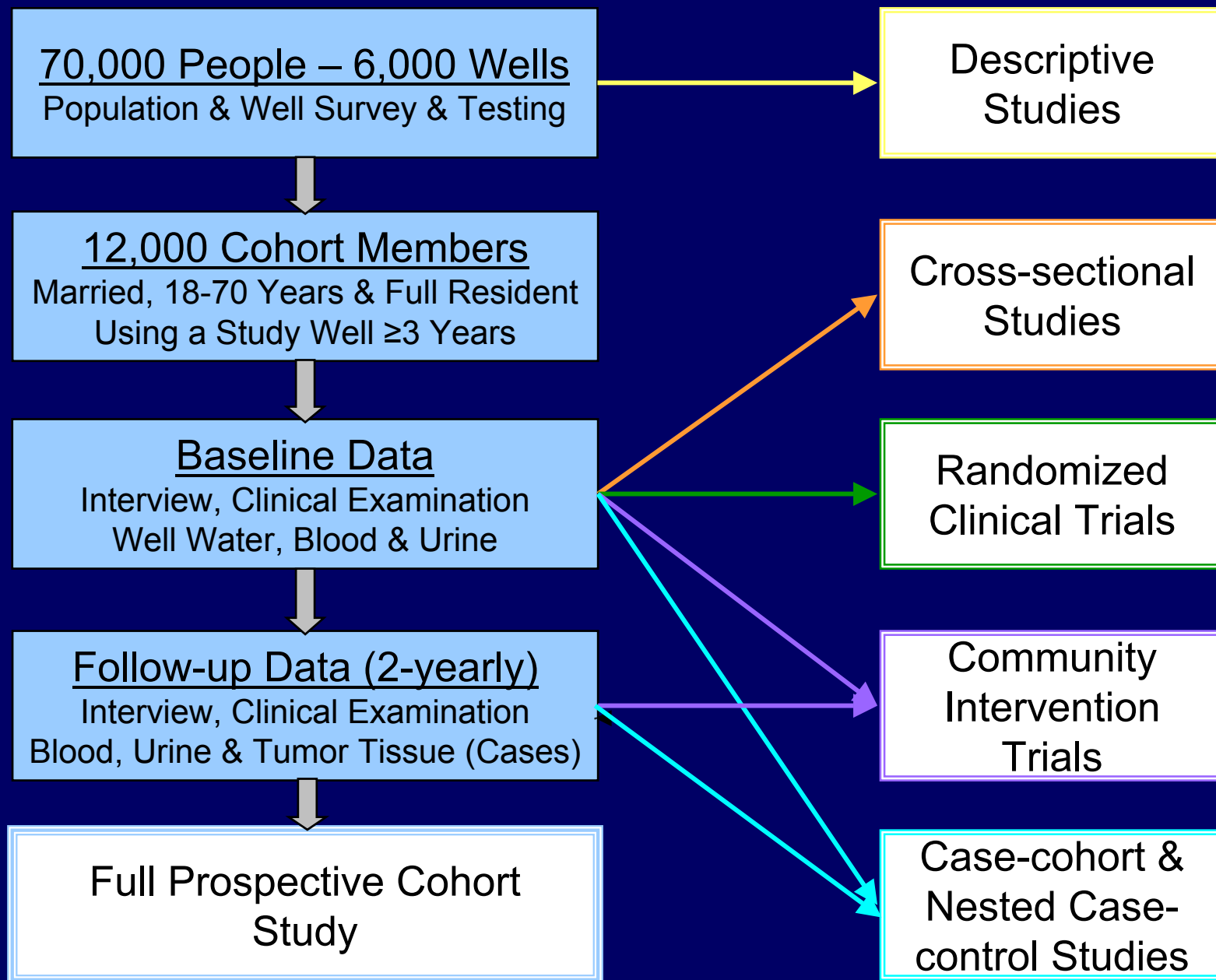
Habibul Ahsan, MD

SBRP Annual Meeting, New York
January 13, 2006



Columbia University Superfund Program Study Area in Araihasar, Bangladesh

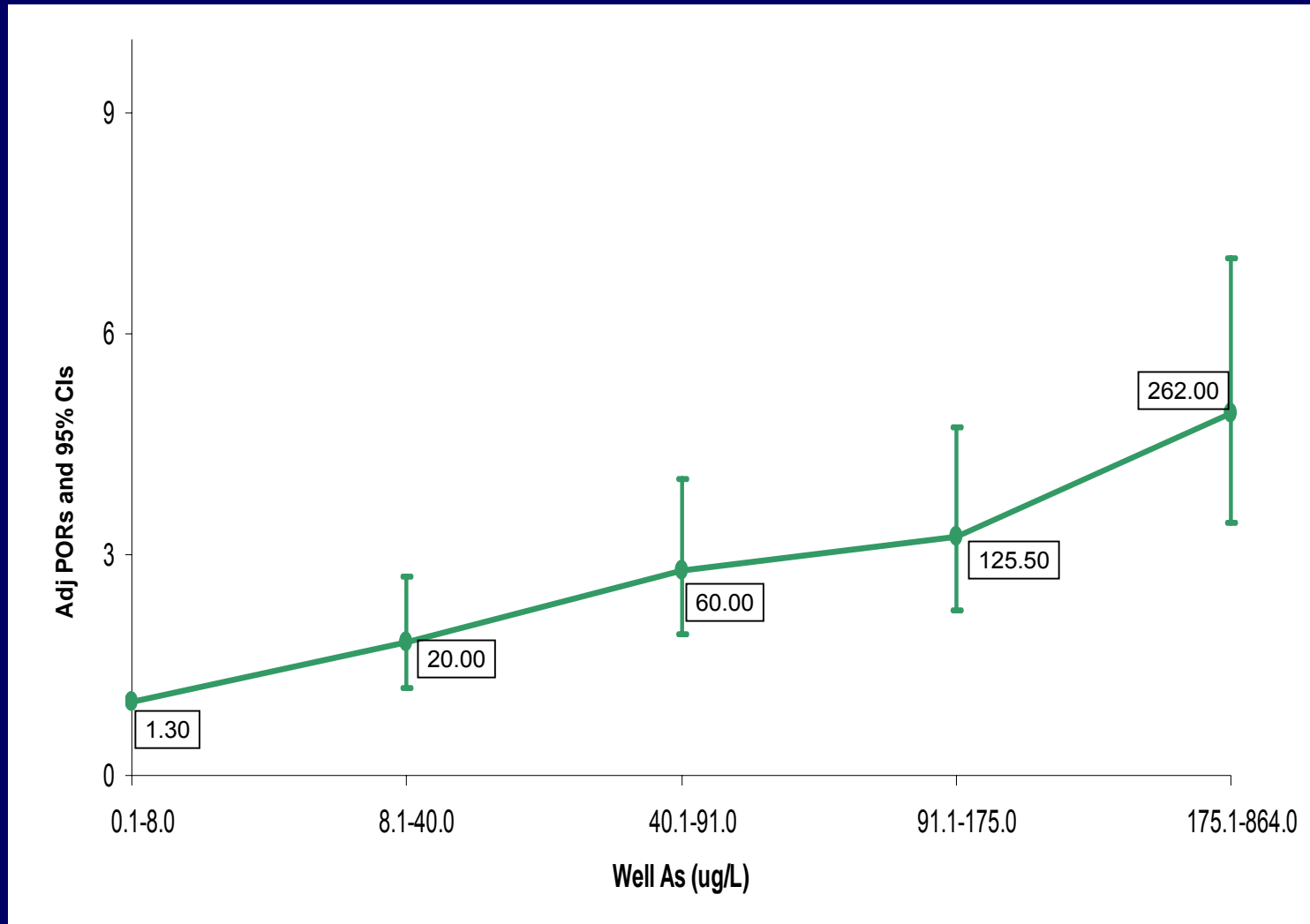
Health Effects of Arsenic Longitudinal Study [HEALS]



Measures of Arsenic Exposure in HEALS

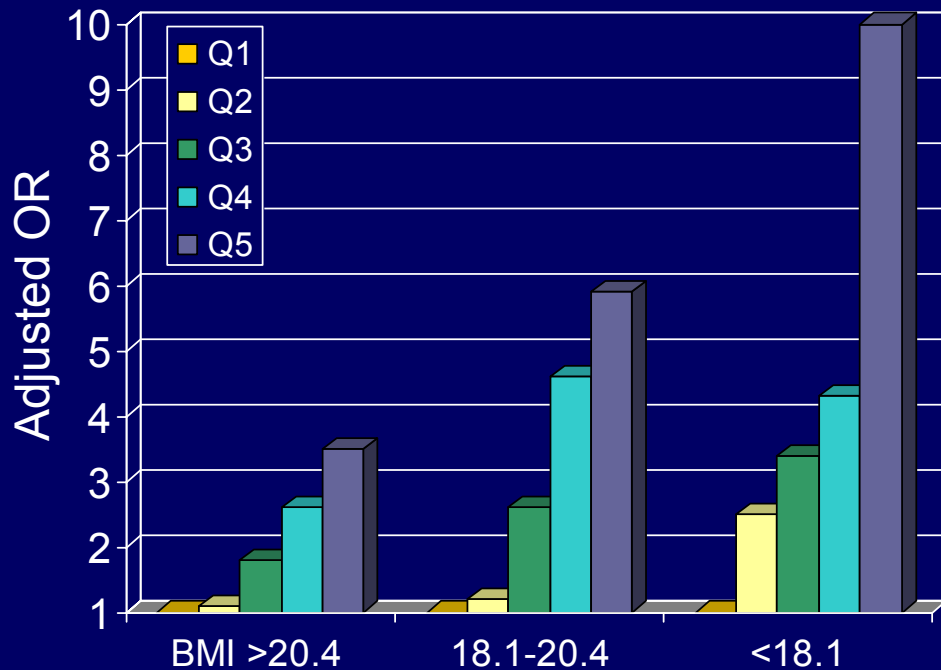
- Well water total As – full cohort
- Time-weighted & Cumulative As indices – full cohort
- Urinary total As (every 2-year) – full cohort
- Blood total As – sub-cohort
- Urinary As species – sub-cohort
- Toe-nail total As & Blood As species – sub-cohort (future)

Risk of Skin Lesions by Well Water Arsenic

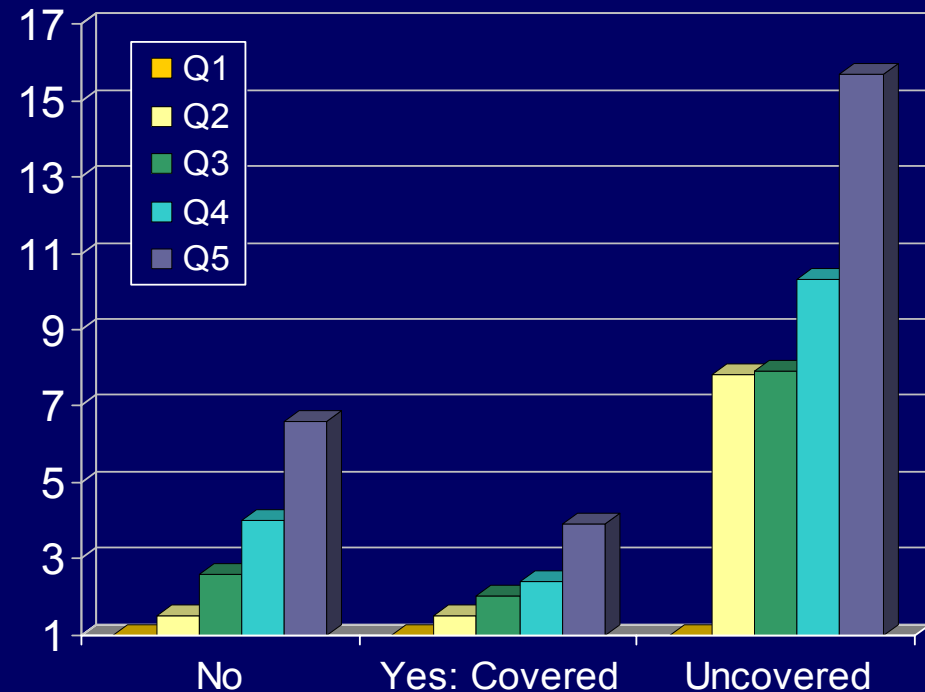


Modifiers of As Effect on Skin Lesions

Influence of BMI

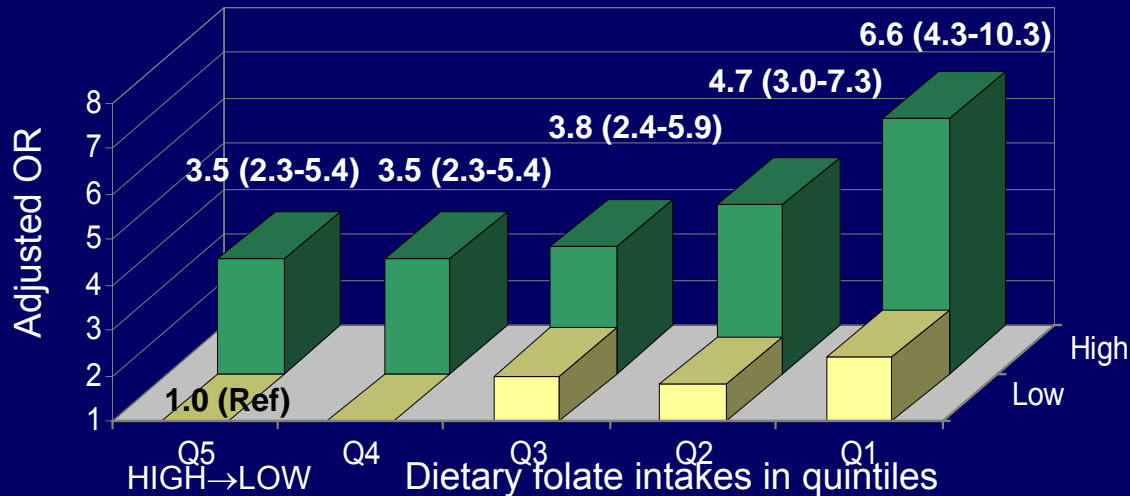
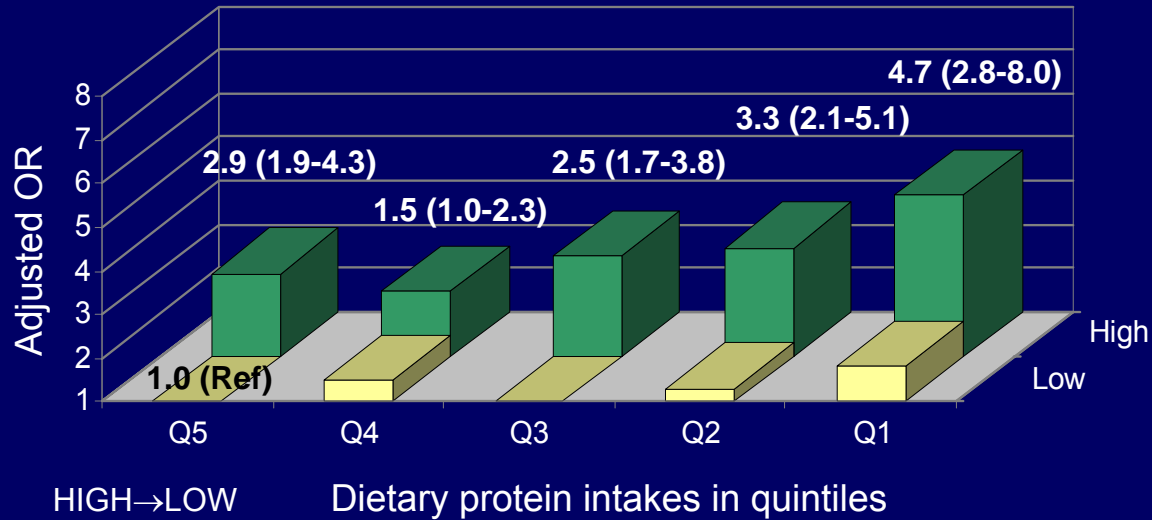


Influence of Sun Exposure



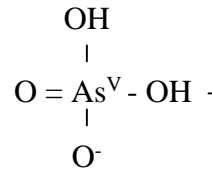
Work outdoor

Influence of Dietary Protein & Folate Intakes on Risk of Arsenic-induced Skin Lesion



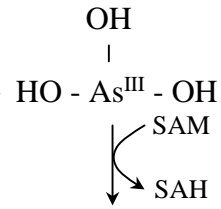
Within Body (Blood & Organs)

Arsenate (As-V)



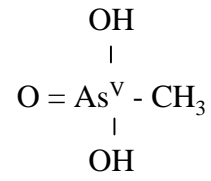
GSH

Arsenite (As-III)



Folate

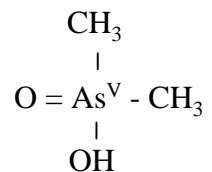
Methylarsonic acid (MMA^V)



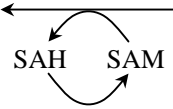
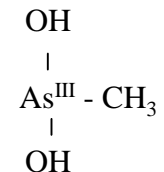
MMA^V Reductase
(GSTO1)

GSH

Dimethylarsinic acid (DMA)



Methylarsonous acid (MMA^{III})



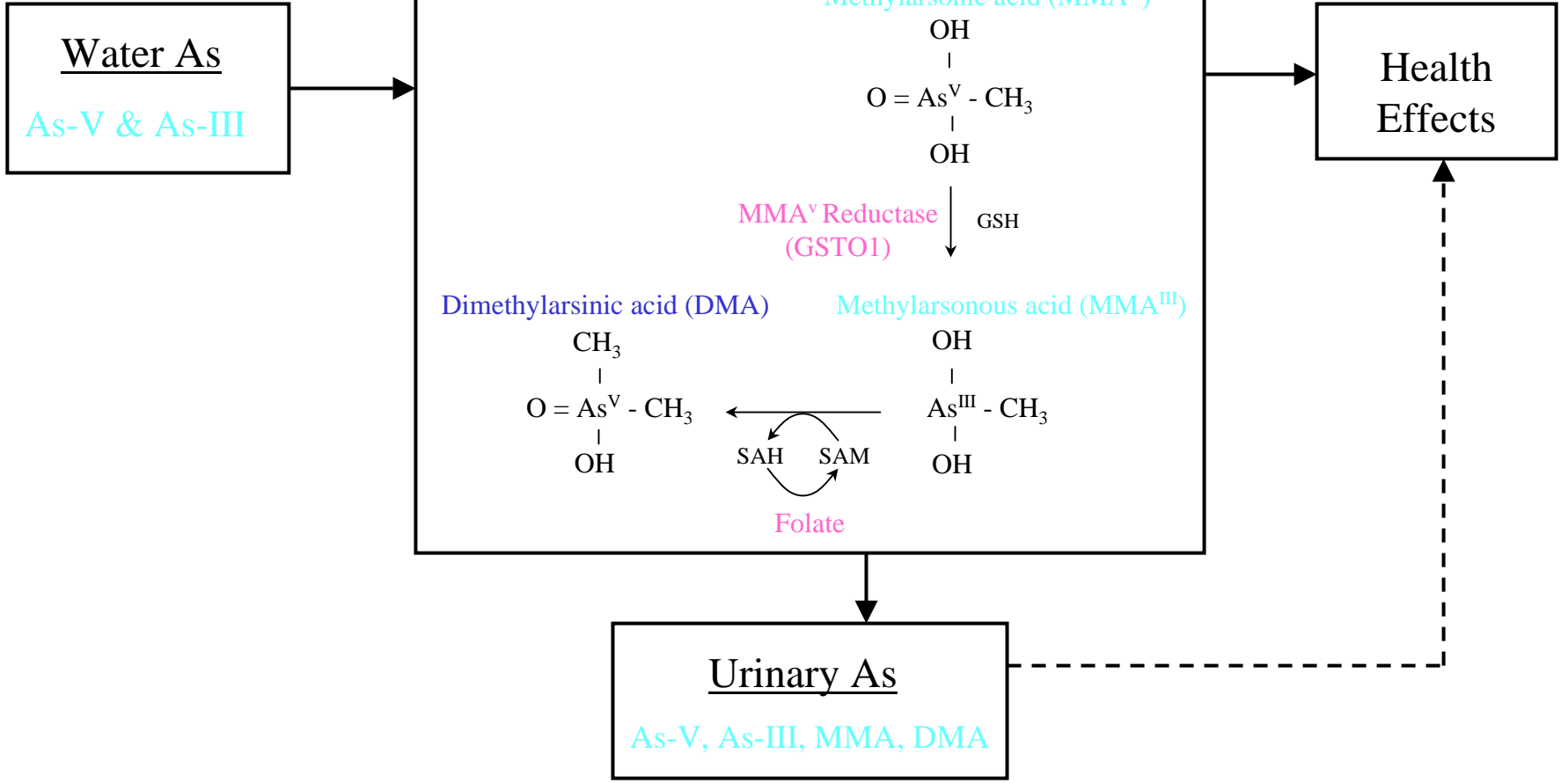
Folate

Water As
As-V & As-III

Health
Effects

Urinary As

As-V, As-III, MMA, DMA



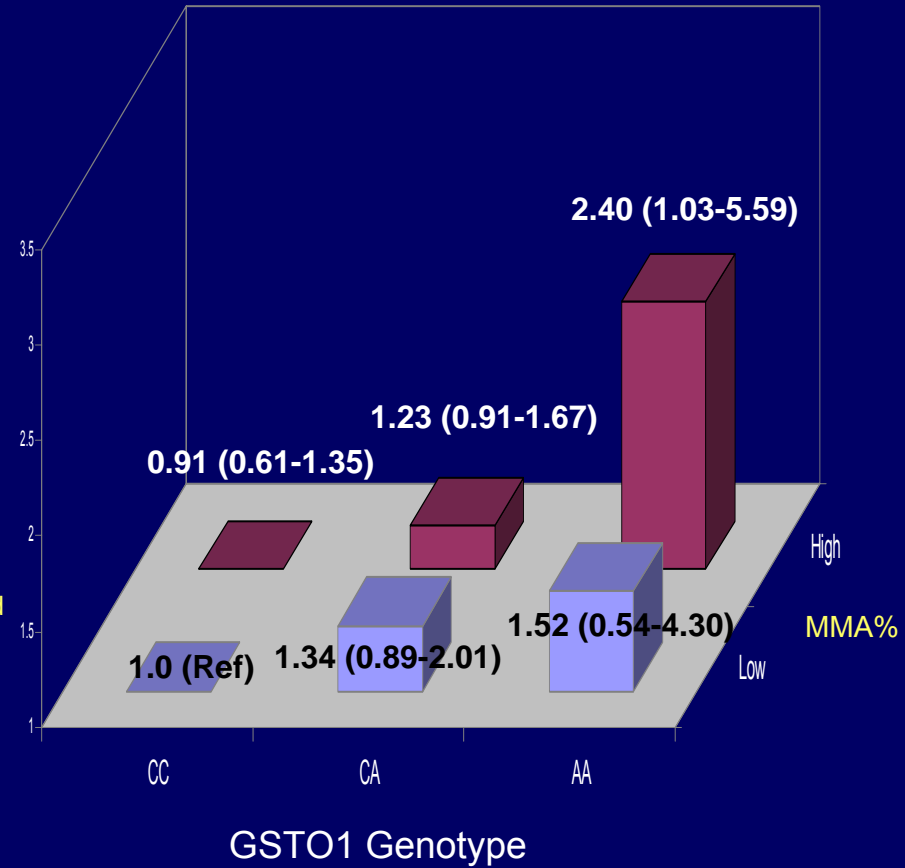
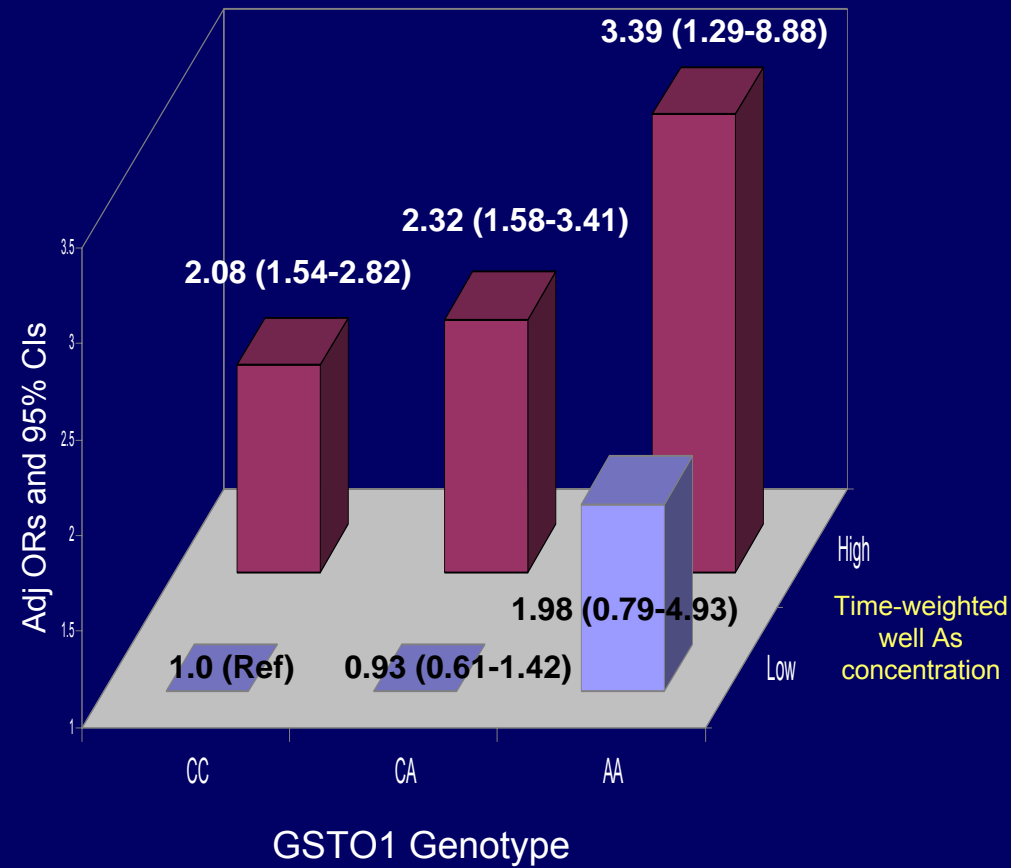
Urinary As Species & Risk of Skin Lesions

Urinary As Species (%)	N		Adjusted ORs for Skin Lesions (95% CI)
	Cases	Controls	
InAs%			
0-12.2	190	344	1.0
12.3-17.1	202	335	1.15 (0.87-1.52)
17.2-69.3	197	355	1.20 (0.91-1.60)
MMA%			
0-10.8	130	406	1.0
10.9-14.9	183	353	1.18 (0.87-1.58)
15.0-33.7	276	275	1.84 (1.37-2.47)
DMA%			
27.9-67.0	232	305	1.0
67.1-74.2	188	346	0.75 (0.58-1.00)
74.3-1.0	169	383	0.73 (0.55-0.96)

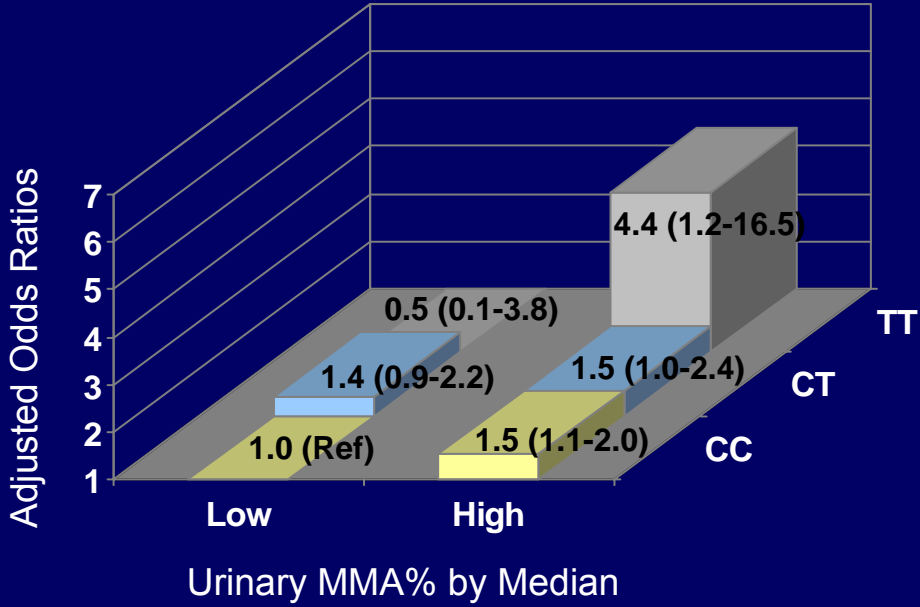
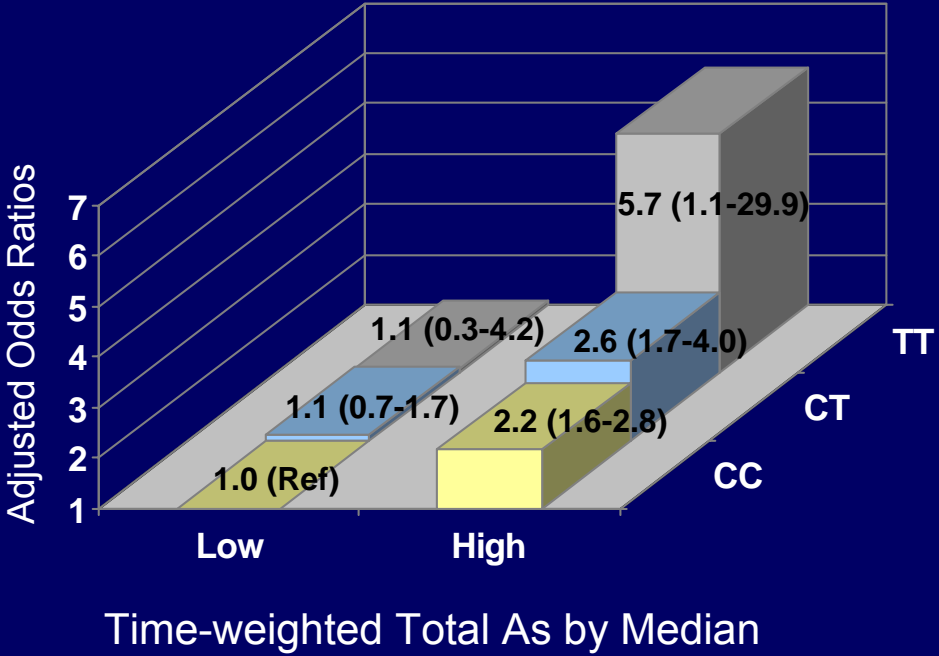
Predictors of Urinary As Species

	DMA%		MMA%	
	Parameter estimates (SE)	P value	Parameter estimates (SE)	P value
BMI	0.130 (0.077)	0.09	-0.067 (0.044)	0.13
Age (years)	0.088 (0.031)	<0.01	0.002 (0.017)	0.17
Gender				
Female	Reference group		Reference group	
Male	-4.554 (0.768)	<0.01	3.625 (0.440)	<0.01
Well water As (per 100 µg/L)	-0.791 (0.298)	<0.01	0.116 (0.170)	0.49
Total urinary As (per 100 µg/L)	-0.435 (0.241)	0.07	0.283 (0.138)	0.04
Urinary creatinine (g)	0.053 (0.006)	<0.01	-0.015 (0.004)	<0.01

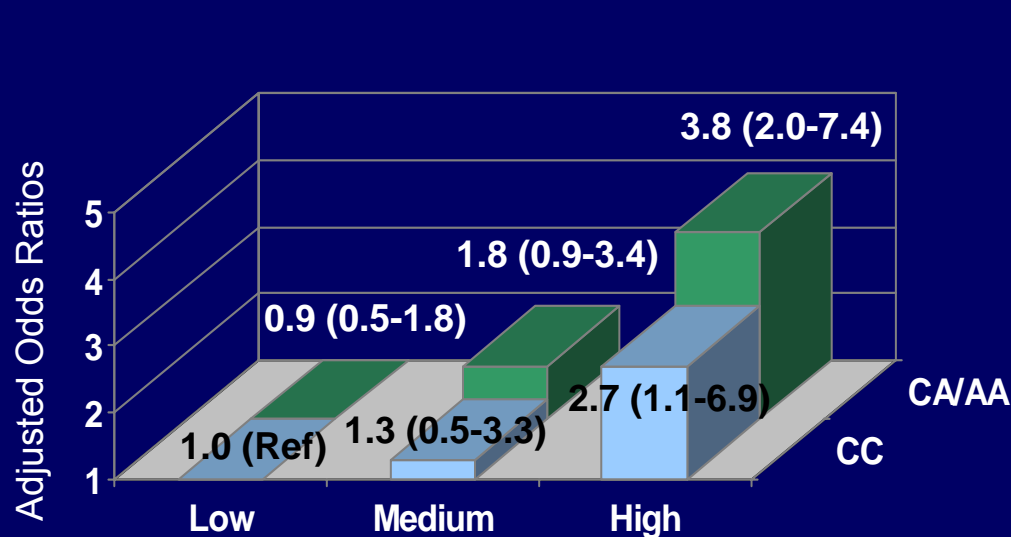
Influence of *GSTO1* Genotype on Risk of Skin Lesion in Relation to Time-weighted As and Urinary MMA%



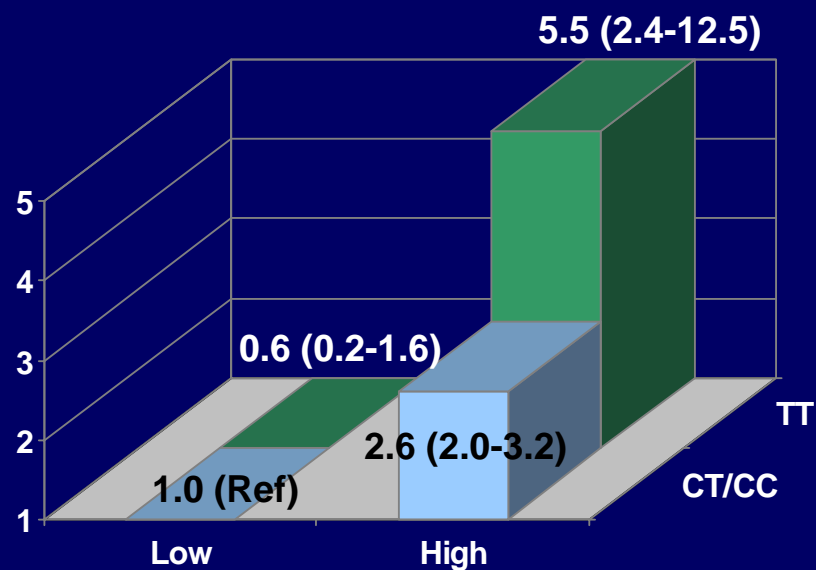
Influence of *MTHFR* C677T Genotype on Risk of Skin Lesion in Relation to Time-weighted As and Urinary MMA%



Influence of *XPD* Codon 751 A-G & *hGPX1* Codon 223 C-T Genotypes on Risk of Arsenic-induced Skin Lesion



Urinary creatinine-adjusted As by tertiles



Urinary creatinine-adjusted As by median

Association Between Arsenic Levels in Water and Urine and Glycosylated Hemoglobin in Blood (HgbA1c%)

Water As & Blood HgbA1c%

	Parameter Estimates	t Value	P-value
Intercept	4.101	83.180	<.0001
9~57 µg/l	0.988	-1.700	0.089
58~138 µg/l	0.994	-0.900	0.366
139~240 µg/l	1.003	0.380	0.703
241~864 µg/l	0.994	-0.930	0.355
BMI	1.005	6.420	<.0001
Education in years	1.000	0.480	0.634
Age in years	1.002	9.200	<.0001
Male	1.018	3.490	0.001
Have TV	1.007	1.480	0.139

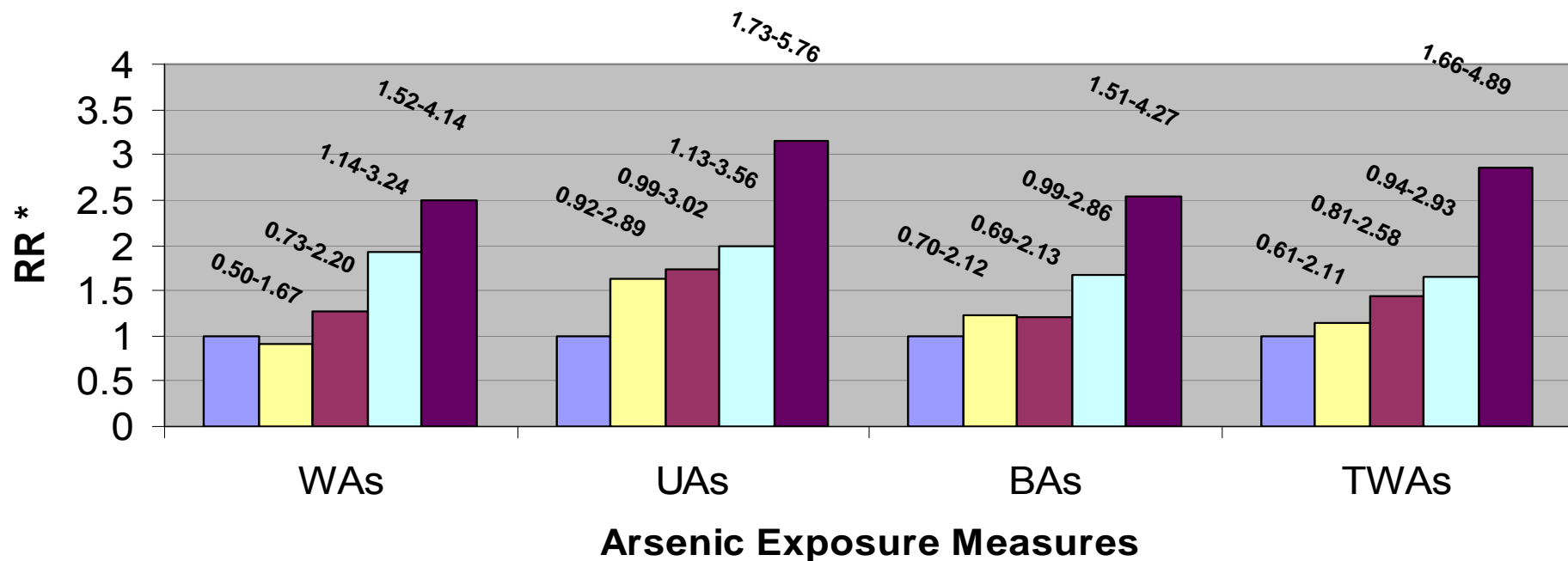
Reference group: 5-8 µg/l. Categories were based on quintiles among the 2102 subjects

Urinary As & Blood HgbA1c%

	Parameter Estimates	t Value	P-value
Intercept	4.082	79.150	<.0001
110~190 µg/g	1.003	0.480	0.631
191~301 µg/g	0.999	-0.170	0.861
302~500 µg/g	0.993	-1.010	0.310
500+ µg/g	1.002	0.290	0.769
BMI	1.005	6.410	<.0001
Education in years	1.000	0.490	0.625
Age in years	1.002	9.210	<.0001
Male	1.017	3.390	0.001
Have TV	1.007	1.430	0.153

Reference group: <110 µg-g creatinine. Categories were based on quintiles among the 2102 subjects

Prospective Association between As exposure Measures & Skin Lesion Risk



RRs adjusted for age, BMI, gender & smoking status
RRs for UAs adjusted for urinary creatinine

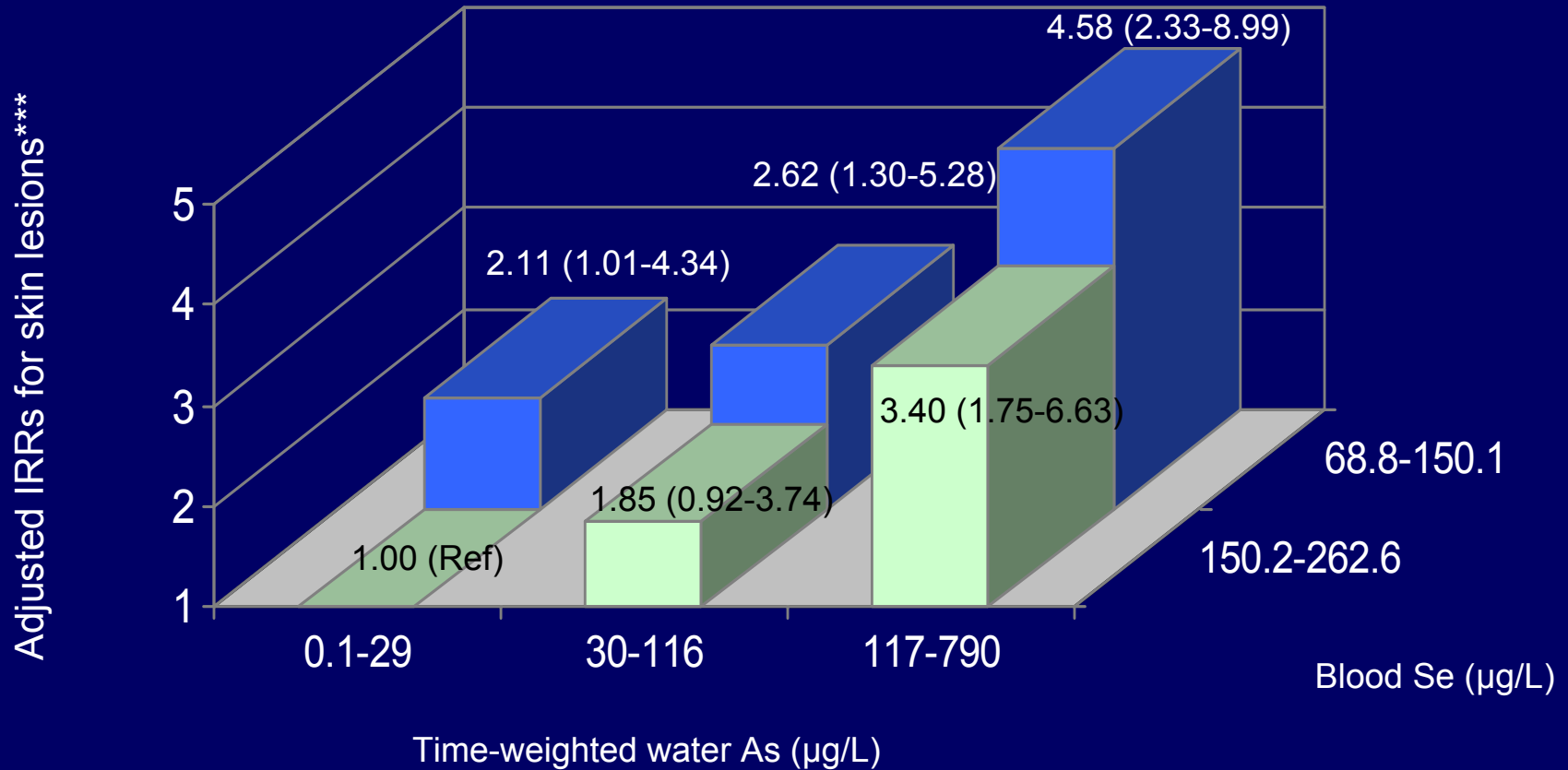
WAs = water arsenic

UAs = total urinary arsenic

BAs = blood arsenic

TWAs = time-weighted arsenic

Joint Effect of As Exposure and Low Blood Se on Risk of Skin Lesion



***Categories of blood Se and time-weighted water As were determined based on tertile and median values, respectively, in the subcohort. IRRs were adjusted for age, BMI, gender, and smoking status

Differentially Expressed Genes in Response to Arsenic Exposure					
Gene symbol	Gene description	GM of:	Skin Lesions	Non-lesions	Ratio of GM*
CXCL2	chemokine (C-X-C motif) ligand 2		42.9	1146.1	0.037
CCL20	chemokine (C-C motif) ligand 20		30.6	522.5	0.059
IL1B	interleukin 1, beta		378.8	4894.3	0.077
ZA20D3	Zinc finger, A20 domain containing 3		46.0	378.5	0.122
SOD2	superoxide dismutase 2, mitochondrial		26.7	239.1	0.112
CD44	CD44 antigen (homing function and Indian blood group system)		60.3	539.3	0.112
CCL3	chemokine (C-C motif) ligand 3		411.0	4513.1	0.091
PTX3	pentraxin-related gene, rapidly induced by IL-1 beta		34.4	416.3	0.083
TNF	tumor necrosis factor (TNF superfamily, member 2)		152.5	1971.2	0.077
KCNJ2	potassium inwardly-rectifying channel, subfamily J, member 2		89.6	889.4	0.101
PAPD4	PAP associated domain containing 4		96.9	612.0	0.158
CCRL2	chemokine (C-C motif) receptor-like 2		84.1	655.2	0.128
IER3	immediate early response 3		401.8	2875.0	0.140
SRP68	signal recognition particle 68kDa		70.2	596.7	0.118
PFKFB3	6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3		100.8	686.9	0.147
PFAAP5	Phosphonoformate immuno-associated protein 5		79.1	466.0	0.170
SOX18	SRY (sex determining region Y)-box 18		73.2	480.2	0.152
HSPA1B	heat shock 70kDa protein 1B		44.4	515.1	0.086
TNFAIP6	tumor necrosis factor, alpha-induced protein 6		55.4	481.6	0.115
SFPQ	Splicing factor proline/glutamine rich		73.1	387.4	0.189
AKAP9	A kinase (PRKA) anchor protein (yotiao) 9		16.1	81.5	0.198
ZNF267	zinc finger protein 267		63.5	351.2	0.181
NR4A2	nuclear receptor subfamily 4, group A, member 2		132.9	783.0	0.170
RFX3	Regulatory factor X, 3 (influences HLA class II expression)		30.3	148.4	0.204

Differentially Expressed Genes in Response to Selenium Treatment

Gene Title

immediate early response 3

interleukin 8

chemokine (C-C motif) ligand 3 /// chemokine (C-C motif) ligand 3-like 1 /// chemokine (C-C motif) ligand 3-like, centromeric

zinc finger protein 91 (HPF7, HTF10)

Kruppel-like factor 12

tumor necrosis factor (TNF superfamily, member 2)

chemokine (C-X-C motif) ligand 2

interleukin 8

putative lymphocyte G0/G1 switch gene

Transformer-2 alpha

inhibitor of DNA binding 2, dominant negative helix-loop-helix protein /// inhibitor of DNA binding 2B, dominant negative helix-loop-helix protein

superoxide dismutase 2, mitochondrial

MRNA; cDNA DKFZp434A202 (from clone DKFZp434A202)

Development and differentiation enhancing factor 1

cold autoinflammatory syndrome 1

serum/glucocorticoid regulated kinase-like

Phosphodiesterase 4B, cAMP-specific (phosphodiesterase E4 dunce homolog, Drosophila)

zinc finger and BTB domain containing 20

Hypothetical protein FLJ43663

interleukin 1, beta

Gene Symbol

IER3

IL8

CCL3 /// CCL3L1 ///
MGC12815

ZNF91

KLF12

TNF

CXCL2

IL8

G0S2

TRA2A

ID2 /// ID2B

SOD2

DDEF1

CIAS1

SGKL

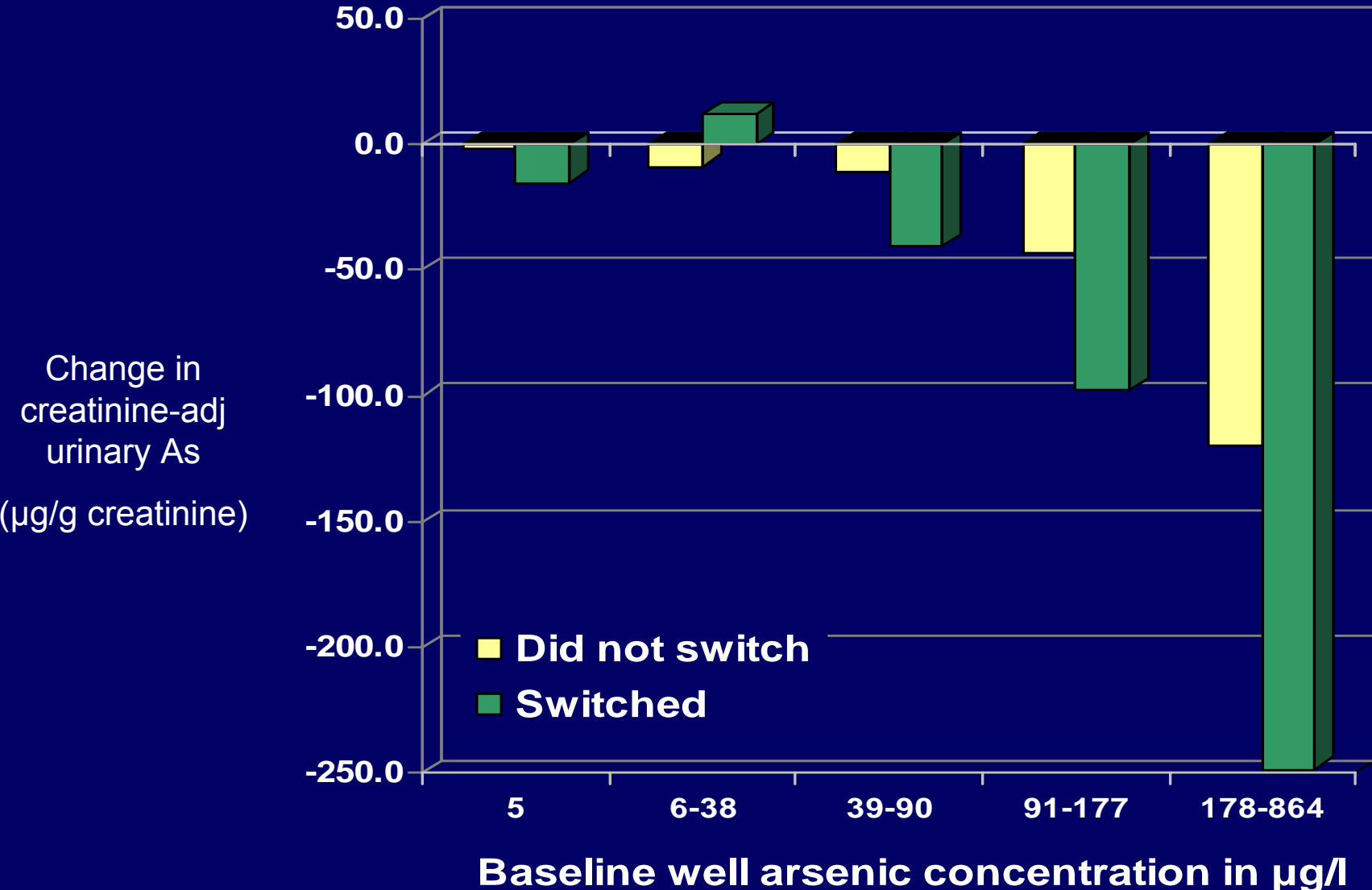
PDE4B

ZBTB20

FLJ43663

IL1B

Changes in Urinary Creatinine-adjusted As (Follow up - Baseline) by Well Switching Status and Baseline Well As



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