Columbia University
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OF PUBLIC HEALTH

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

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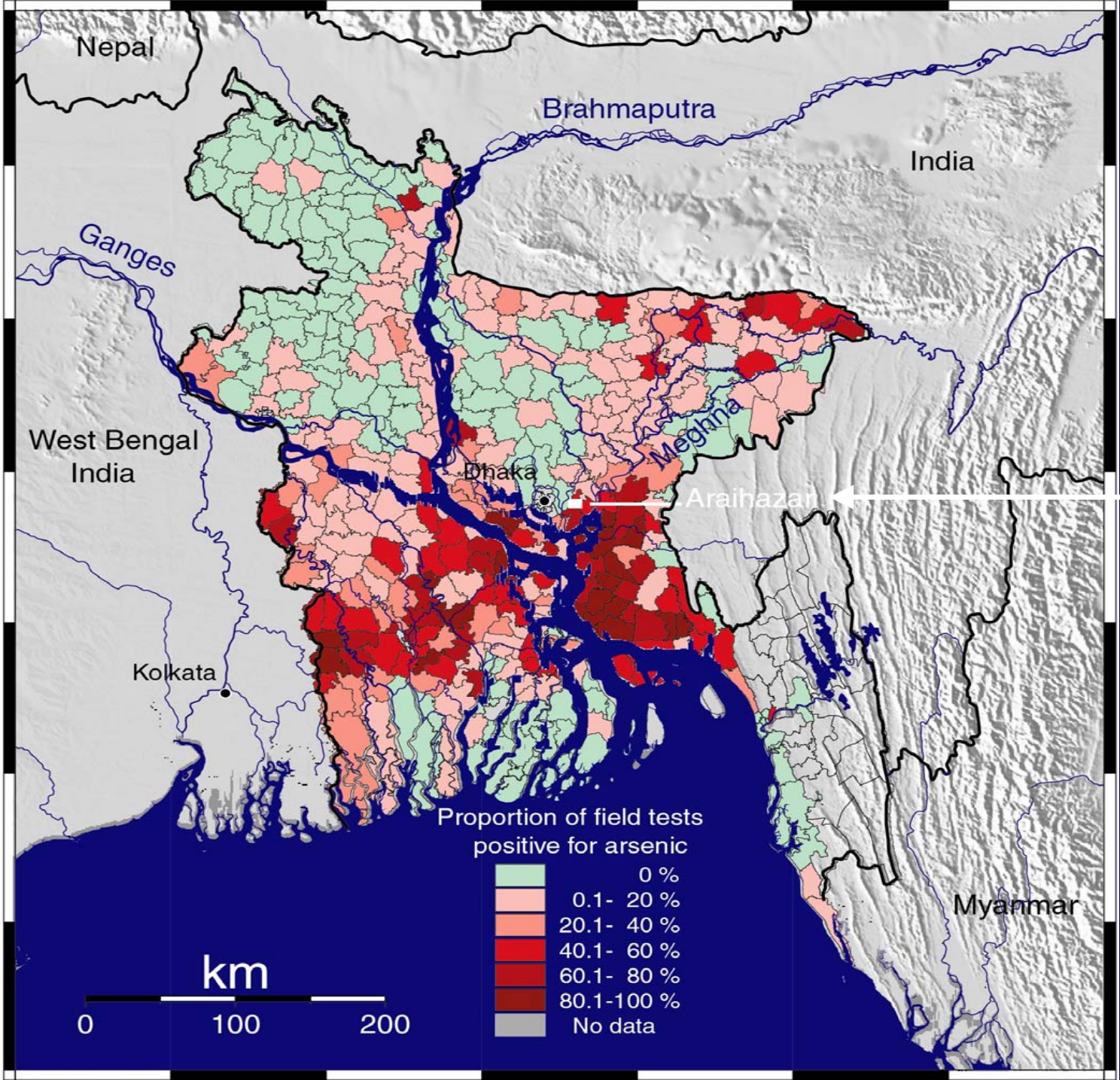
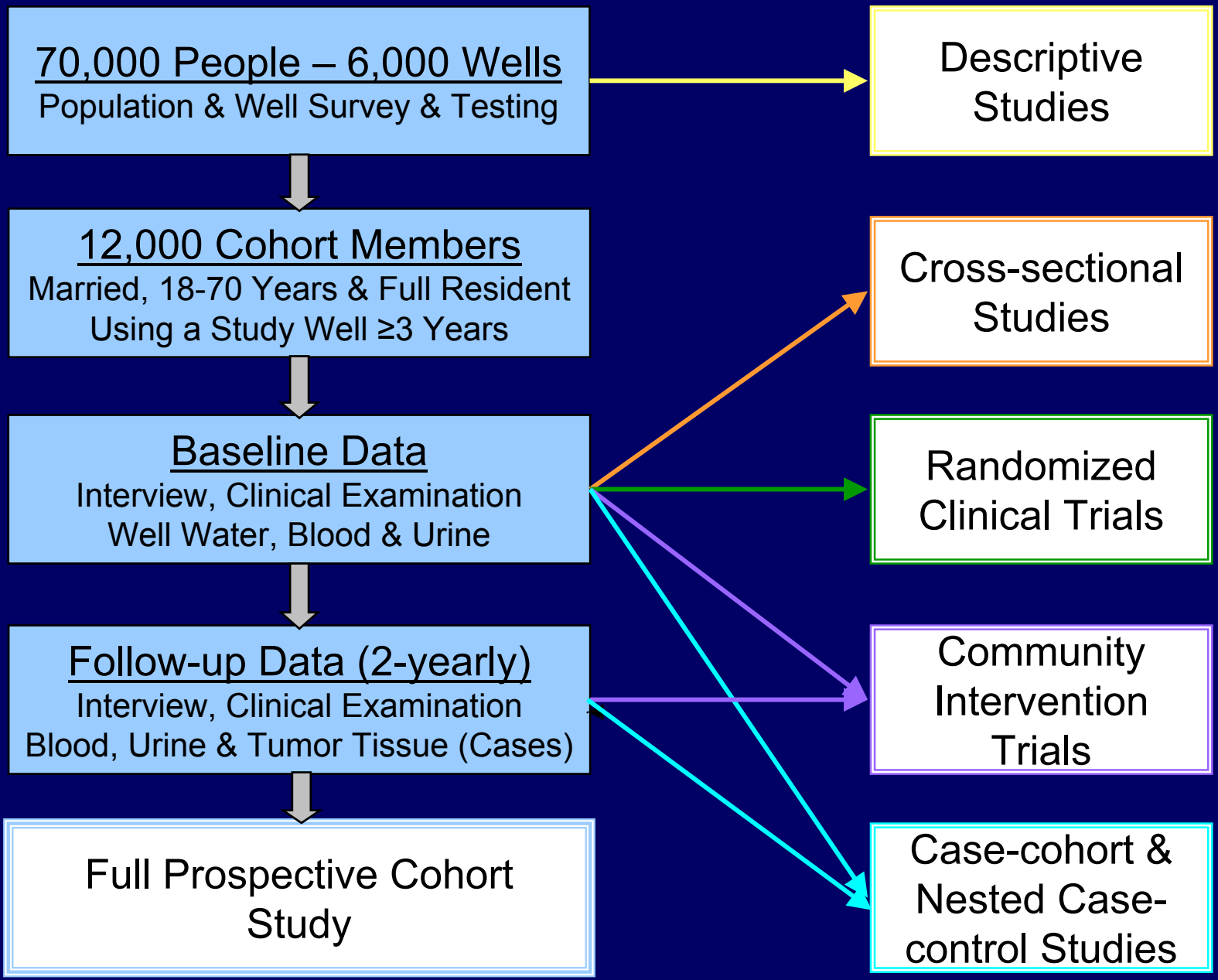
SBRP Annual Meeting, New York
January 13, 2006



Columbia University Superfund Program Study Area in Araihazar, Bangladesh

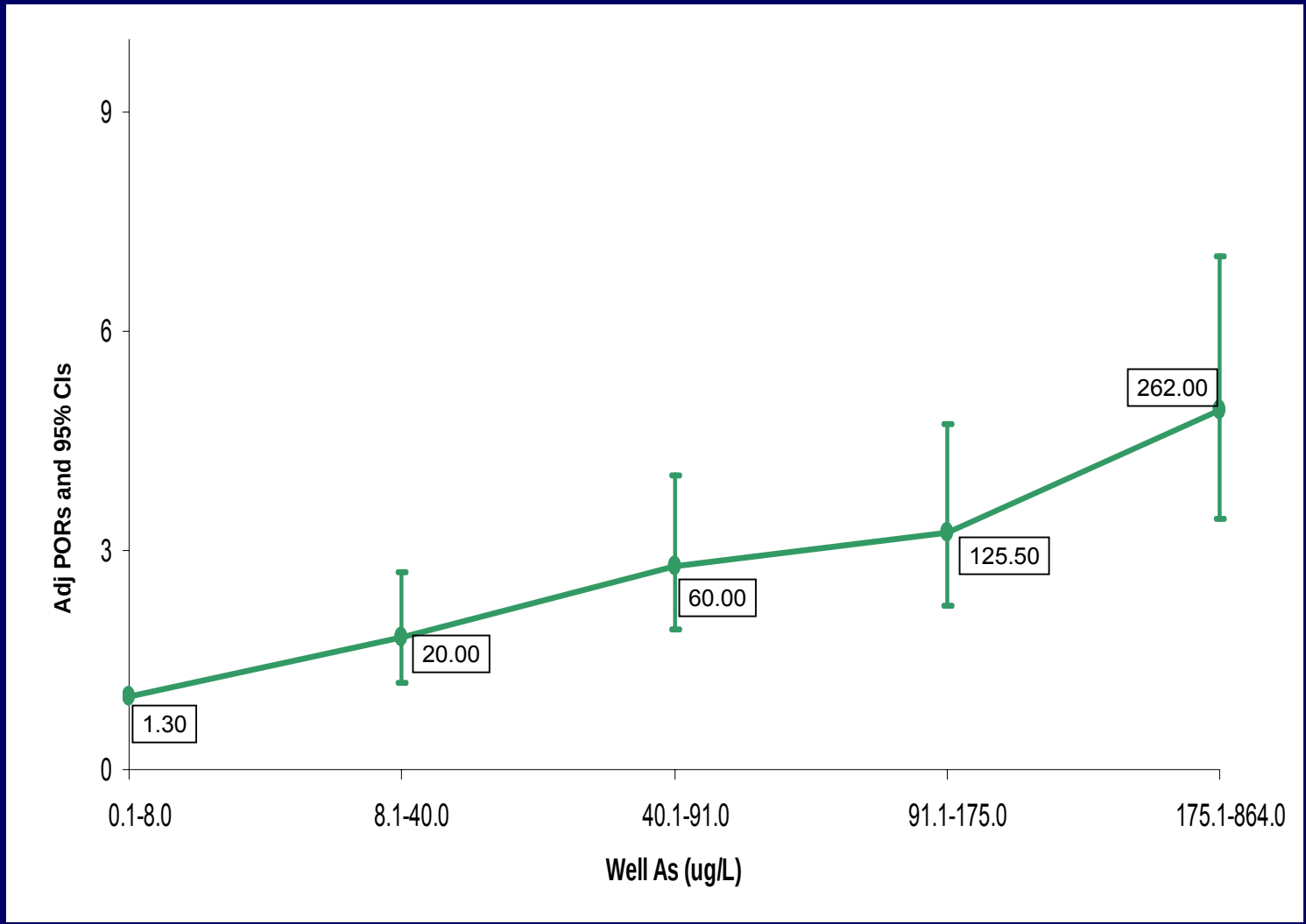
Health Effects of Arsenic Longitudinal Study [HEALS]



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)

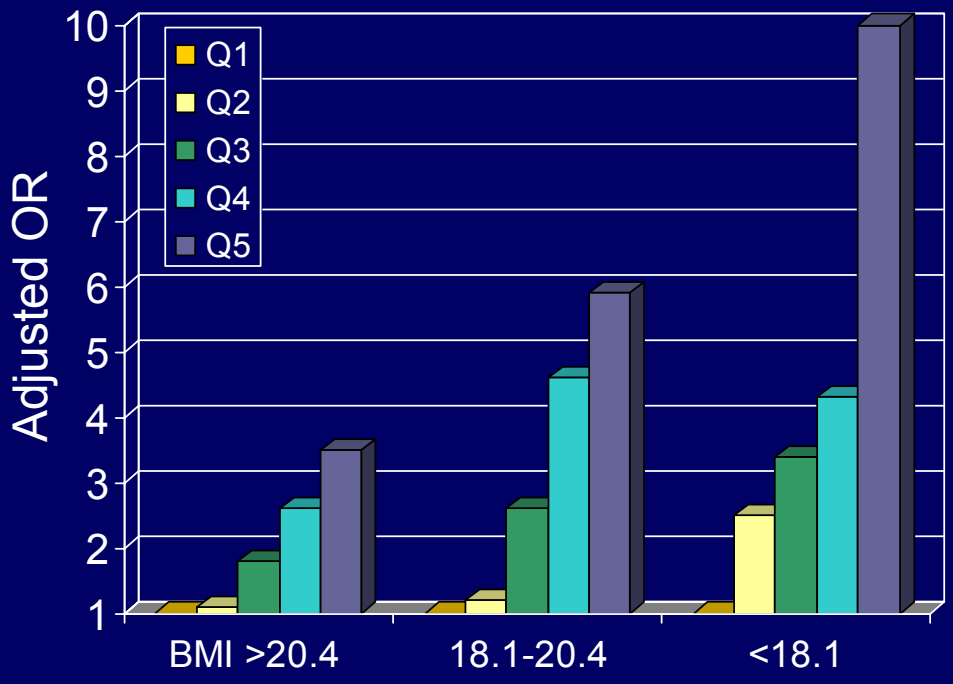
Risk of Skin Lesions by Well Water Arsenic



Ahsan et al., Am J Epidemiol, In press

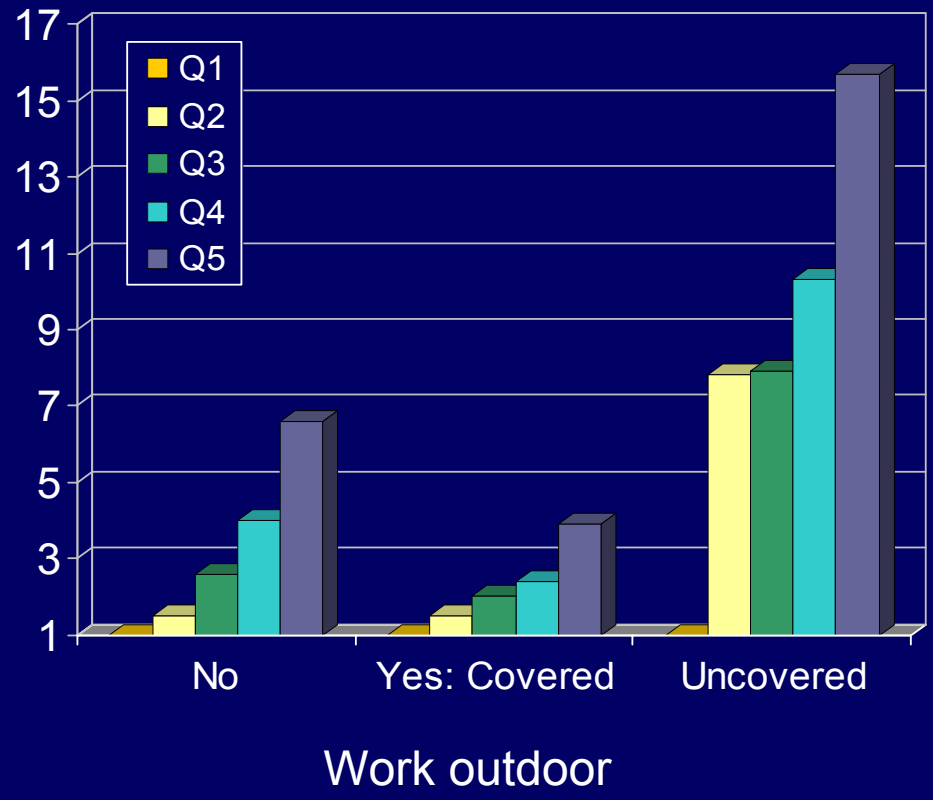
Modifiers of As Effect on Skin Lesions

Influence of BMI



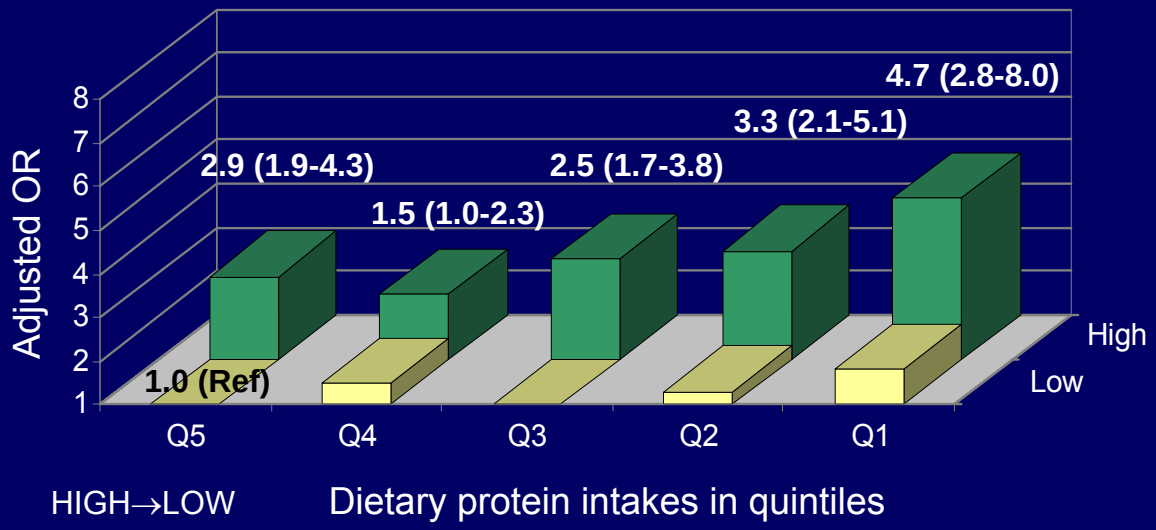
Ahsan et al., Am J Epidemiol, In press

Influence of Sun Exposure

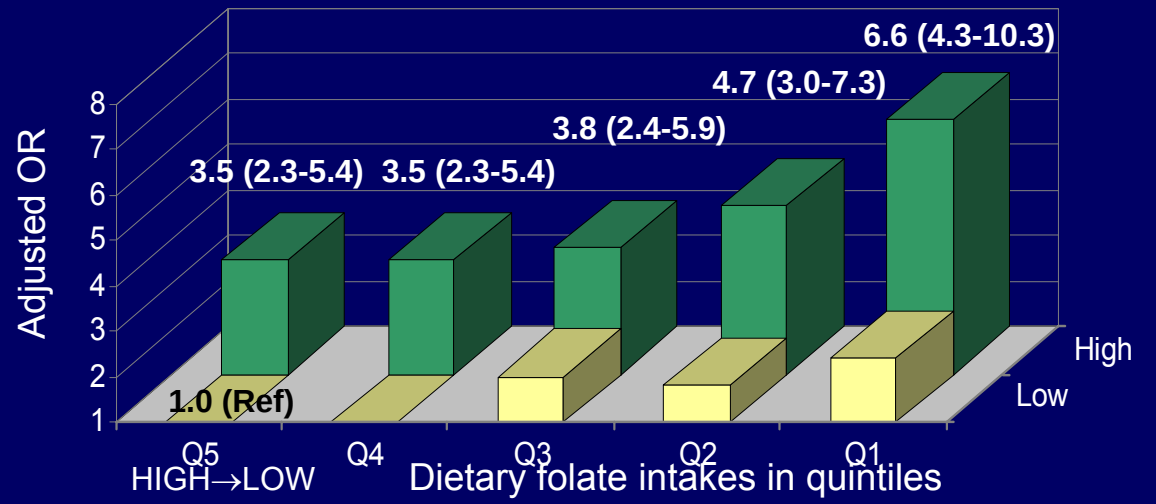


Chen et al., Epidemiology, In Press

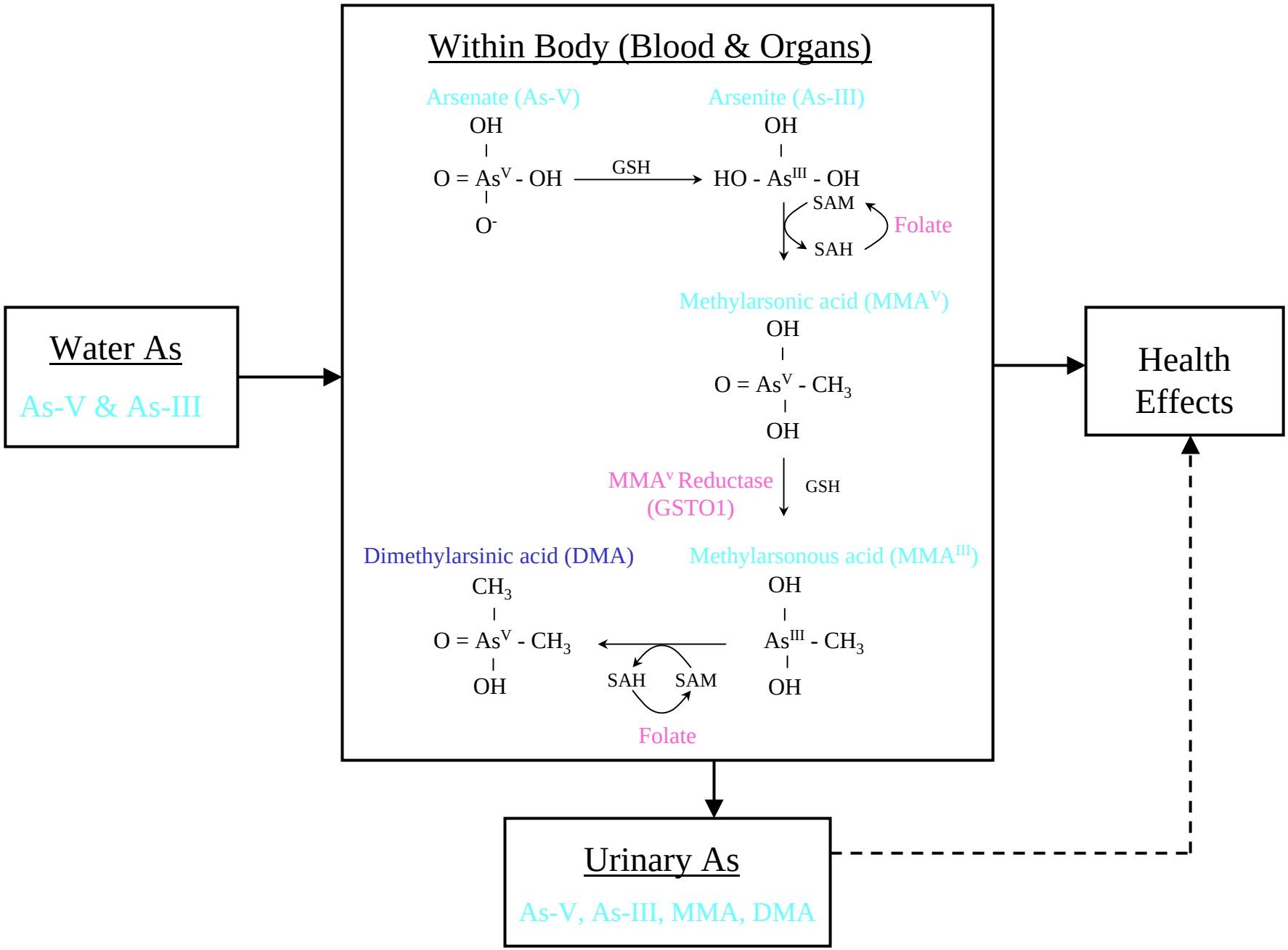
Influence of Dietary Protein & Folate Intakes on Risk of Arsenic-induced Skin Lesion



Urinary creatinine-adjusted As by median



Urinary creatinine-adjusted As by median


Water As
As-V & As-III
Within Body (Blood & Organs)
Arsenate (As-V)
Arsenite (As-III)
GSH
SAM
SAH
Folate
Methylarsonic acid (MMA^V)
MMA^V Reductase
(GSTO1)
GSH
Dimethylarsinic acid (DMA)
Methylarsonous acid (MMA^{III})
SAH
SAM
Folate
Health Effects
Urinary As
As-V, As-III, MMA, DMA

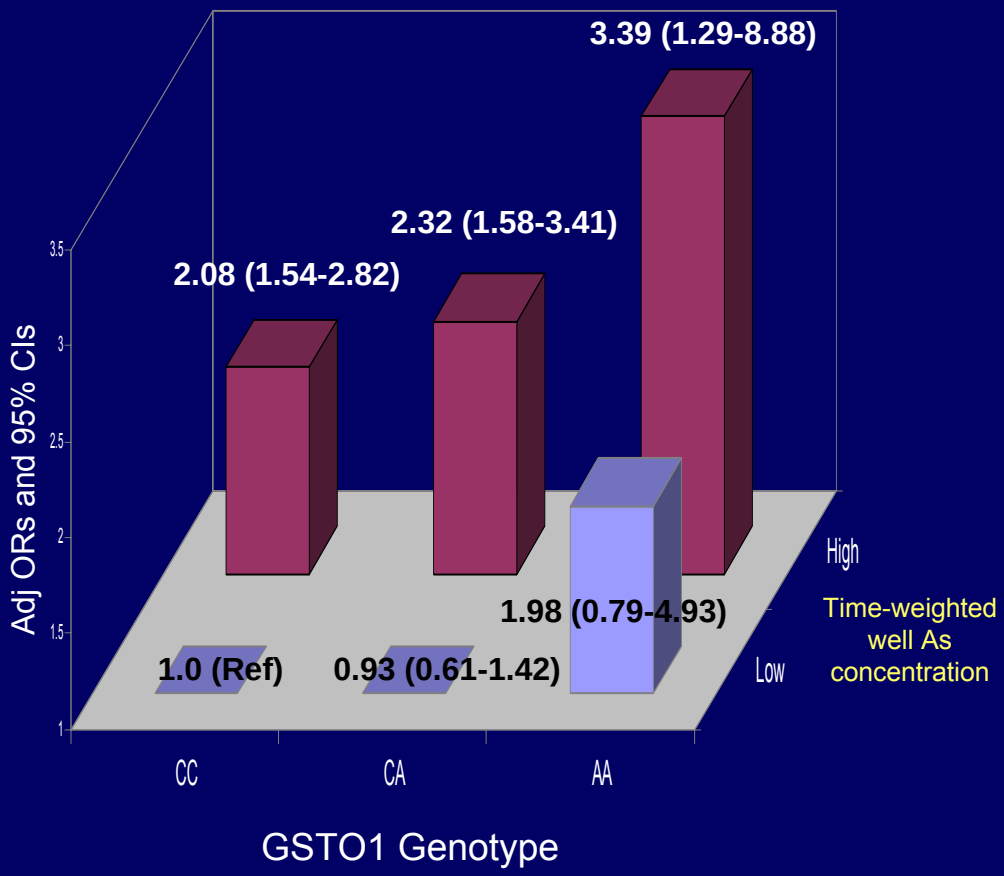
Urinary As Species & Risk of Skin Lesions

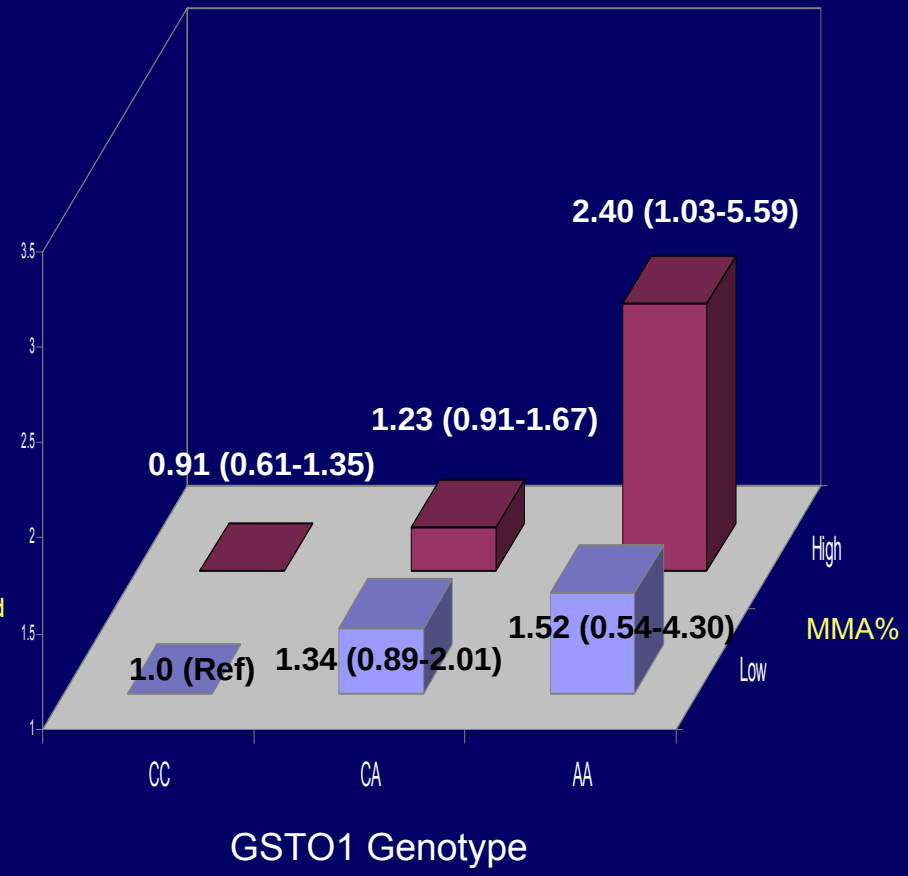
Urinary As Species (%)	N		Adjusted ORs for Skin Lesions (95% CI)
	Cases	Controls	
InAs%			
0-12.2	190	344	1.0
12.3-17.1	202	335	1.15 (0.87-1.52)
17.2-69.3	197	355	1.20 (0.91-1.60)
MMA%			
0-10.8	130	406	1.0
10.9-14.9	183	353	1.18 (0.87-1.58)
15.0-33.7	276	275	1.84 (1.37-2.47)
27.9-67.0	232	305	1.0
67.1-74.2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

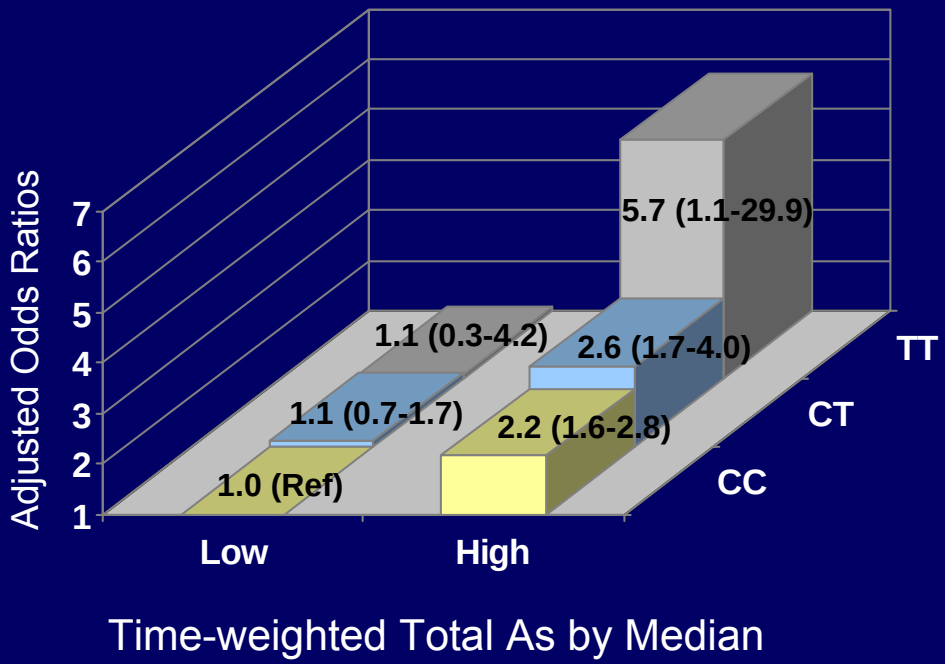
	DMA%		MMA%	
	Parameter estimates (SE)	P value	Parameter estimates (SE)	P value
BMI	0.130 (0.077)	0.09	-0.067 (0.044)	0.13
Age (years)	0.088 (0.031)	**<0.01**	0.002 (0.017)	0.17
Gender				
Female	Reference group		Reference group	
Male	-4.554 (0.768)	**<0.01**	3.625 (0.440)	**<0.01**
Well water As (per 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**

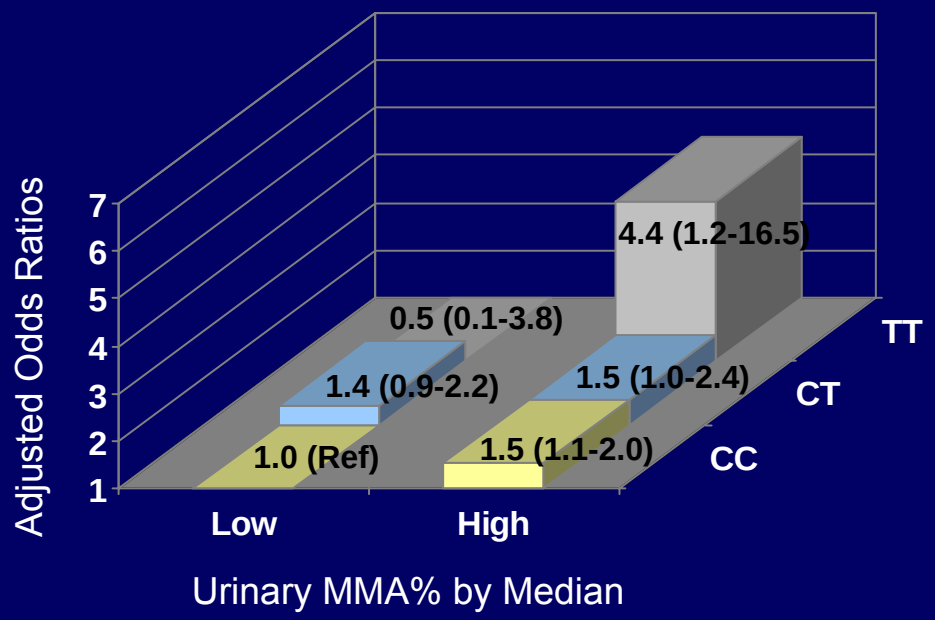
Influence of *GSTO1* Genotype on Risk of Skin Lesion in Relation to Time-weighted As and Urinary MMA%



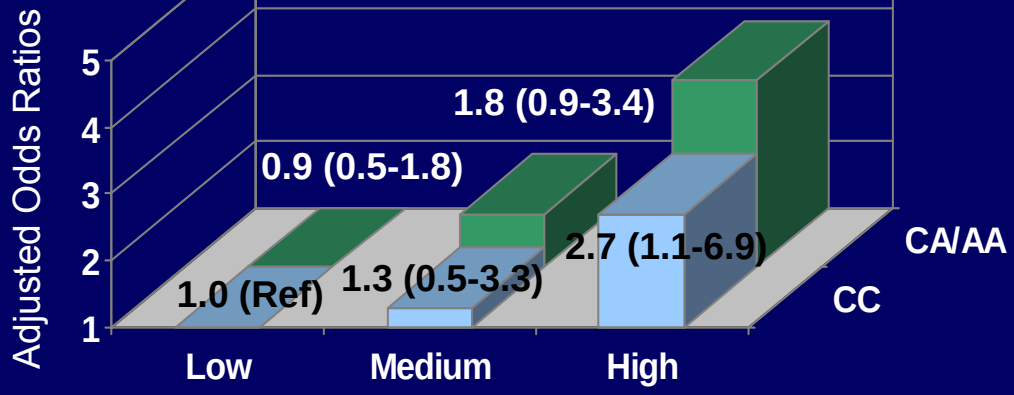


Influence of *MTHFR* C677T Genotype on Risk of Skin Lesion in Relation to Time-weighted As and Urinary MMA%

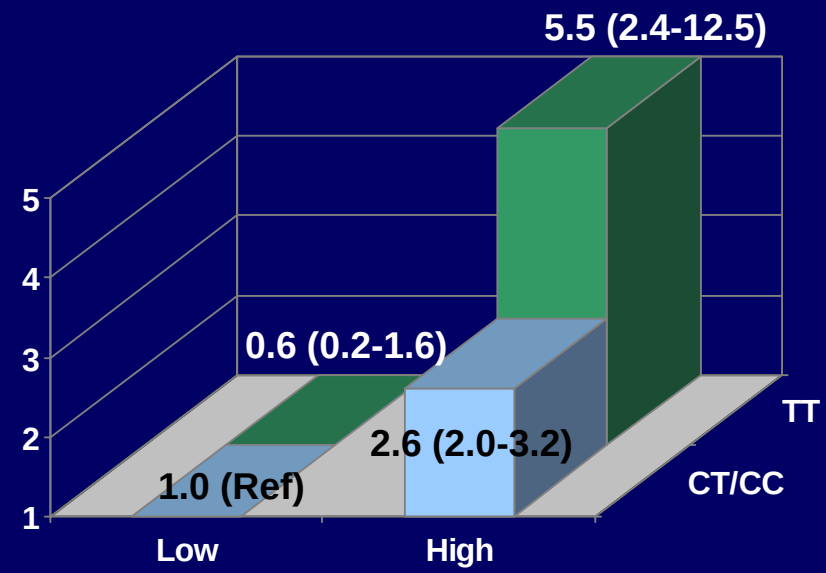




Influence of *XPD* Codon 751 A-G & *hGPX1* Codon 223 C-T Genotypes on Risk of Arsenic-induced Skin Lesion



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

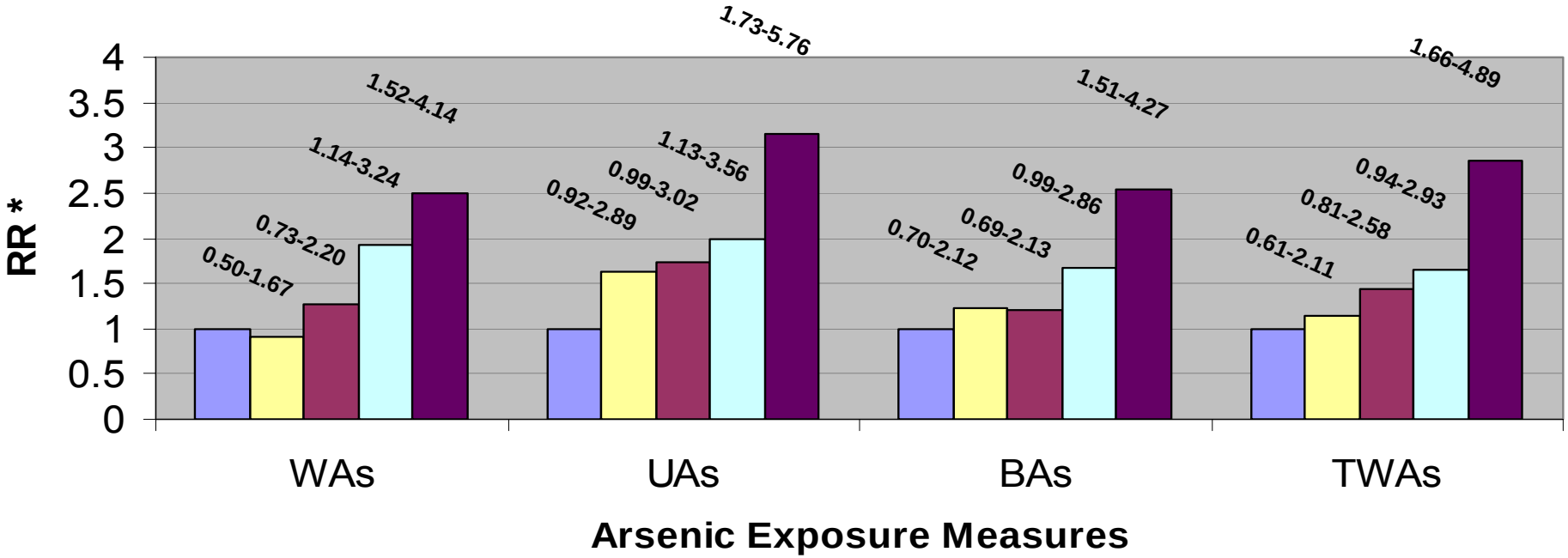
Reference group: 5-8 µg/l. Categories were based on quintiles among the 2102 subjects

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

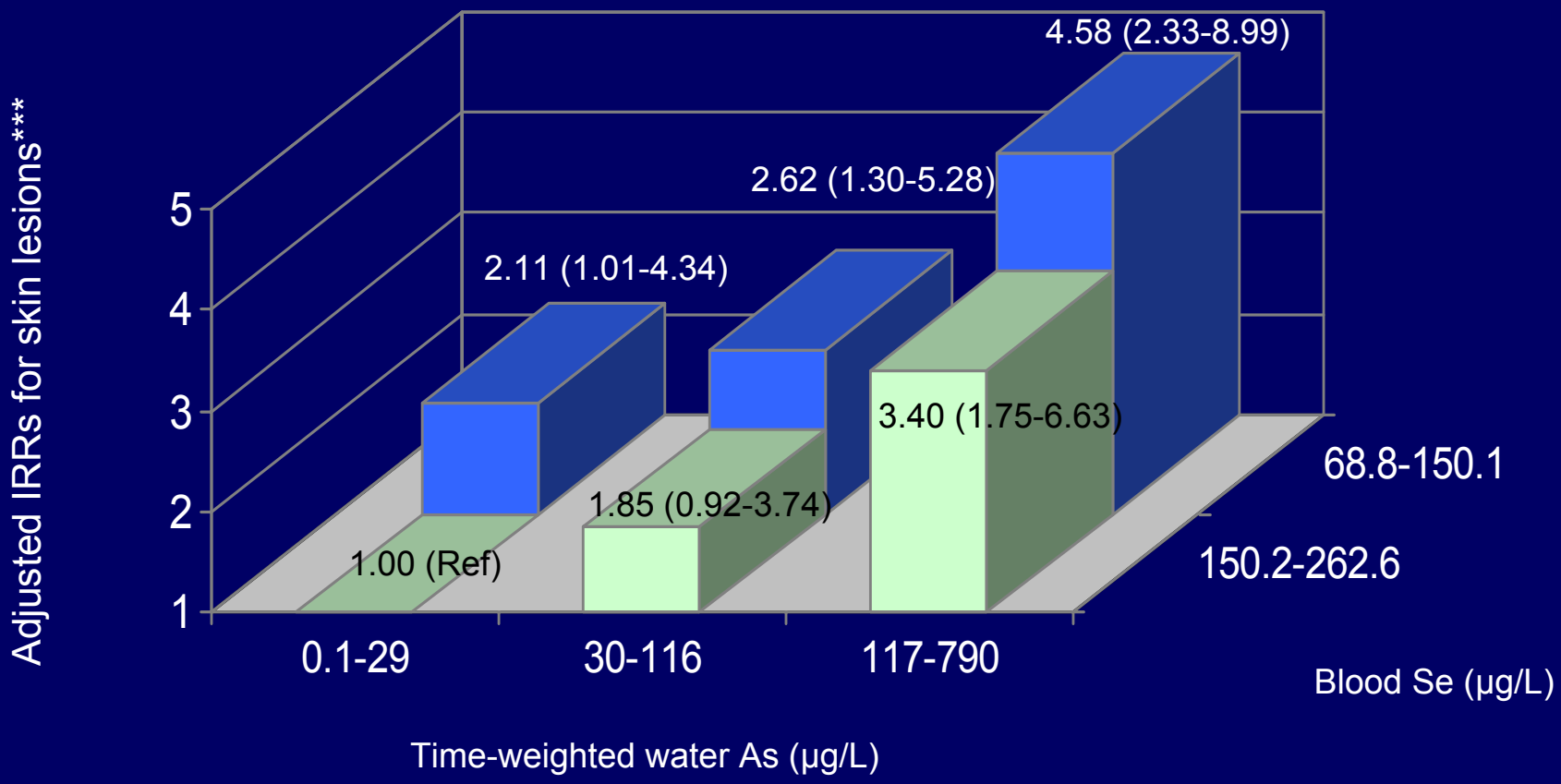
Prospective Association between As exposure Measures & Skin Lesion Risk



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

WAs = water arsenic
UAs = total urinary arsenic
BAs = bloodarsenic
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	Gene Symbol
immediate early response 3	IER3
interleukin 8	IL8
chemokine (C-C motif) ligand 3 /// chemokine (C-C motif) ligand 3-like 1 /// chemokine (C-C motif) ligand 3-like, centromeric	CCL3 /// CCL3L1 /// MGC12815
zinc finger protein 91 (HPF7, HTF10)	ZNF91
Kruppel-like factor 12	KLF12
tumor necrosis factor (TNF superfamily, member 2)	TNF
chemokine (C-X-C motif) ligand 2	CXCL2
interleukin 8	IL8
putative lymphocyte G0/G1 switch gene	G0S2
Transformer-2 alpha	TRA2A
inhibitor of DNA binding 2, dominant negative helix-loop-helix protein /// inhibitor of DNA binding 2B, dominant negative helix-loop-helix protein	ID2 /// ID2B
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superoxide dismutase 2, mitochondrial	SOD2
MRNA; cDNA DKFZp434A202 (from clone DKFZp434A202)	---
Development and differentiation enhancing factor 1	DDEF1
cold autoinflammatory syndrome 1	CIAS1
serum/glucocorticoid regulated kinase-like	SGKL
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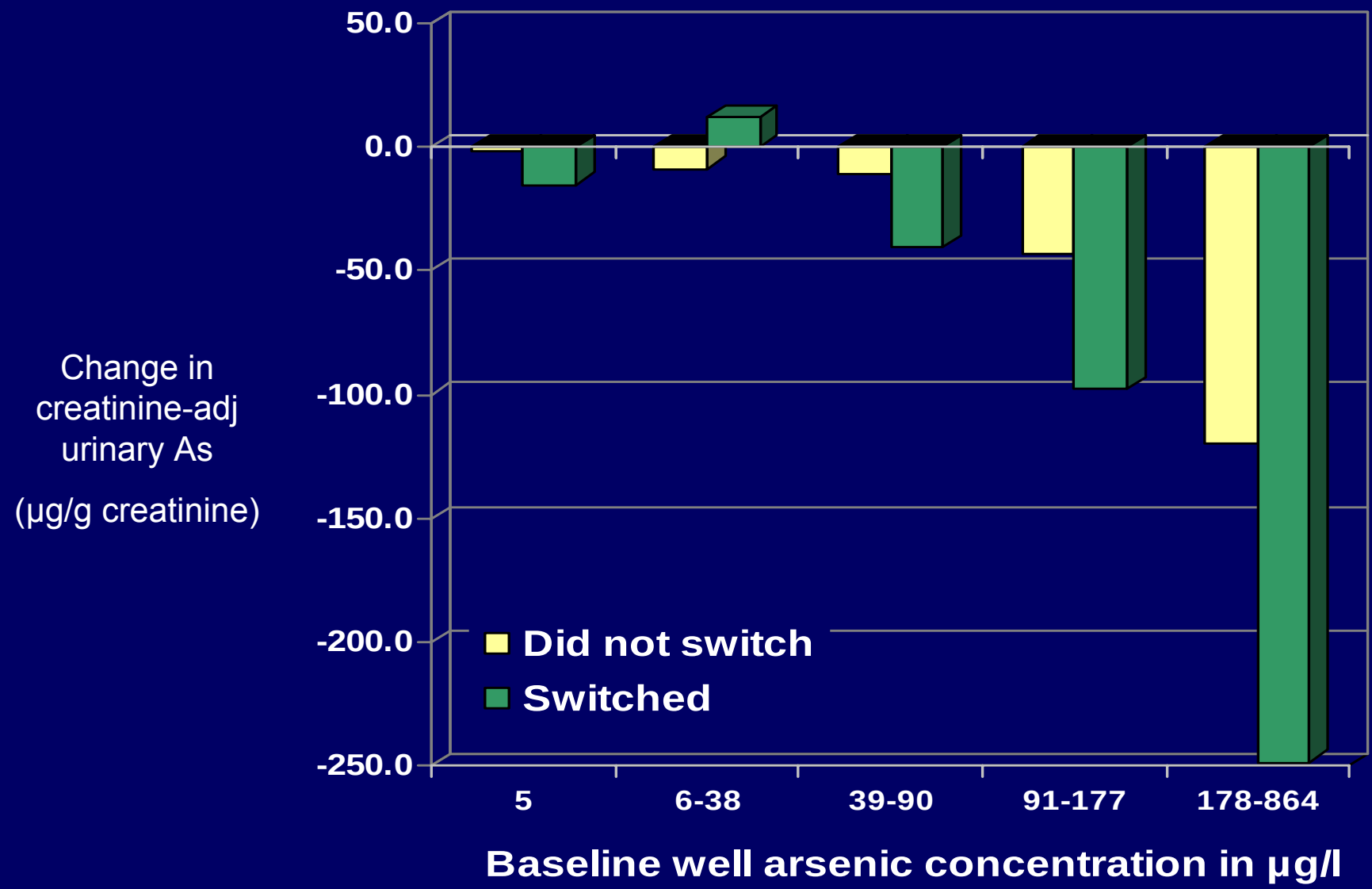
Phosphodiesterase 4B, cAMP-specific (phosphodiesterase E4 dunce homolog, Drosophila)	PDE4B
zinc finger and BTB domain containing 20	ZBTB20
Hypothetical protein FLJ43663	FLJ43663
interleukin 1, beta	IL1B

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



Acknowledgements

Bangladesh

Dr. Tariqul Islam
Dr. Mahmudur Rahman
Dr. AZM Iftikhar Hussain
Dr. Mahfuzar Rahman

&

32 Member Field Team

Special Thanks to:
Residents of Araihazar

Columbia University

Health Sciences
Joseph Graziano, PhD
Yu Chen, PhD
Faruque Parvez, MS, MPH
Maria Argos, MPH
Muhammad Kibriya, MD, PhD
Farzana Jasemine, MD, PhD
Diane Levy, MS
Marni Hall, MPH
Wei-Yann Tsai, PhD
Mary Gamble, PhD
Regina Santella, PhD
Paul Brandt-Rauf, MD, DrPH
Geoffrey Howe, PhD

Earth Sciences
Lex van Geen, PhD
Yan Zheng, PhD
James Simpson, PhD
Martin Stute, PhD