

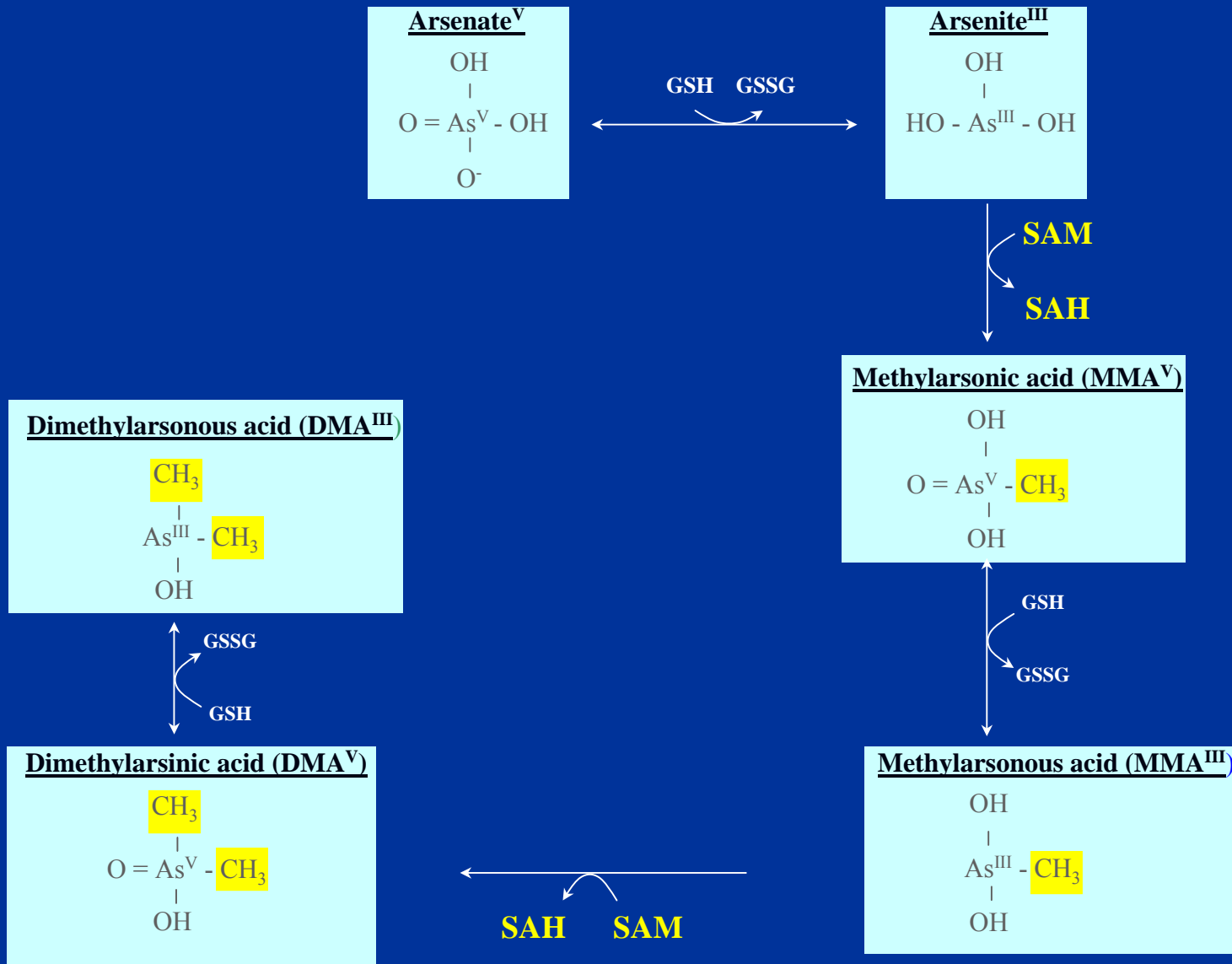
**Folate and Arsenic Metabolism:
A double-blind placebo controlled
folate supplementation trial in
Bangladesh.**

J. Richard Pilsner, MPH, MPhil

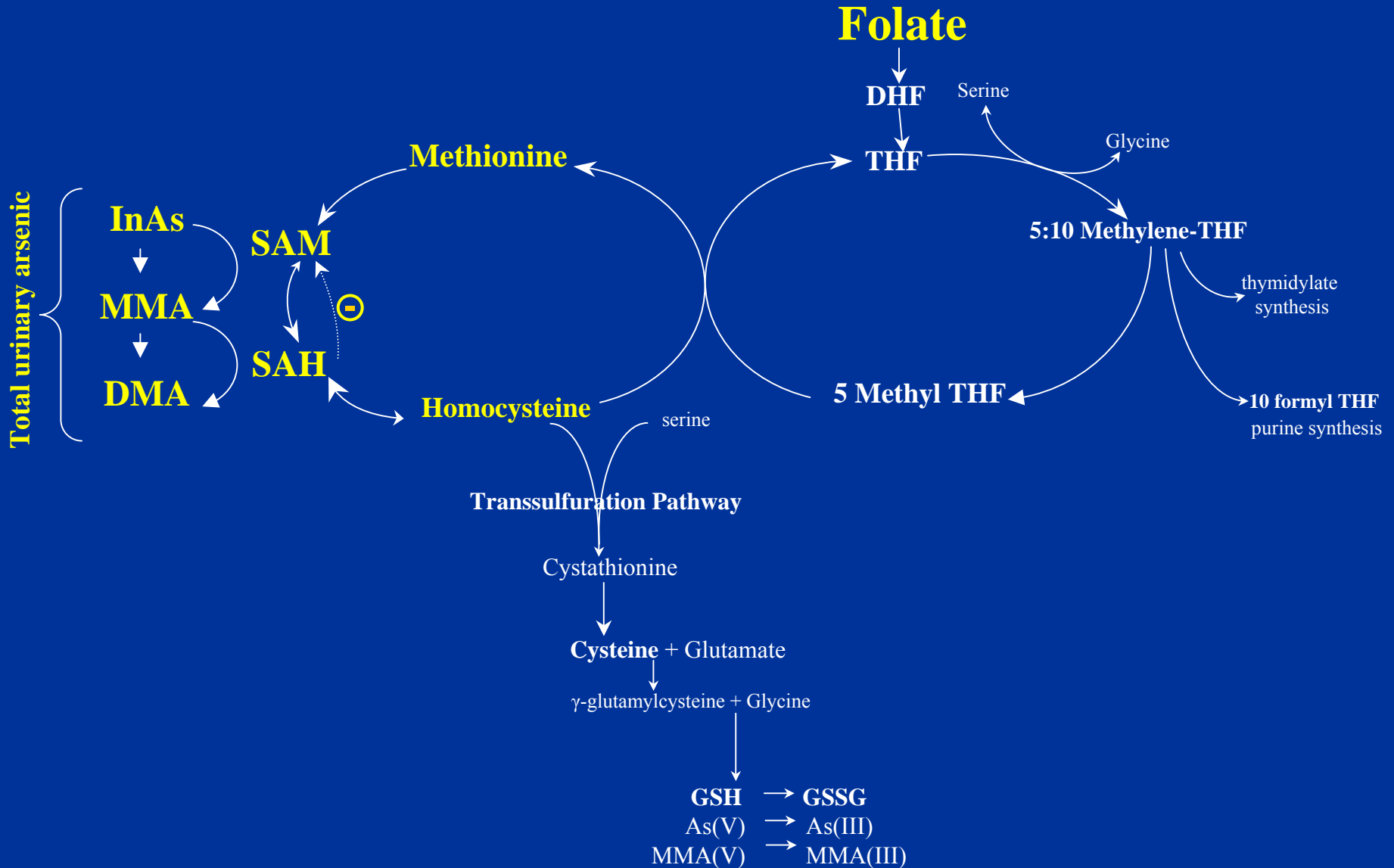
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Arsenic metabolism by mono- and dimethylation.



Overview of One-Carbon Metabolism



Background: Arsenic Methylation & Folate

■ Animal studies

- Dietary folate deficiency

- *Toxicol.Lett. 2003: 145:167-74*

- Dietary methyl donor deficiency

- *Mutat Res 1997: 386:315-34*

**Decrease total
urinary arsenic
excretion,
particularly DMA**

■ Case-control studies in Taiwan

- Lower DMA in urine increased the risk of skin and bladder cancers and peripheral vascular disease

J Occup environ Med 2003, 45:241-8

Cancer Epidemiol Biomarker Prev 1997: 589-96

Toxicol Appl Pahrmacol 2005, 206: 299-308

Background: Arsenic Methylation in Bangladesh

- Prospective cohort
 - Increase %MMA in urine is a risk factor for skin lesions
- Cross-Sectional Study

	%InAs	%MMA	%DMA
Folate (nM)	-0.12*	-0.12*	0.14*
Homocysteine (μM)	0.06	0.21#	-0.14**

Spearman correlation coefficients * p < 0.05, ** p < 0.001, # p < 0.001

Placebo-controlled Folate Intervention Trial

Hypothesis

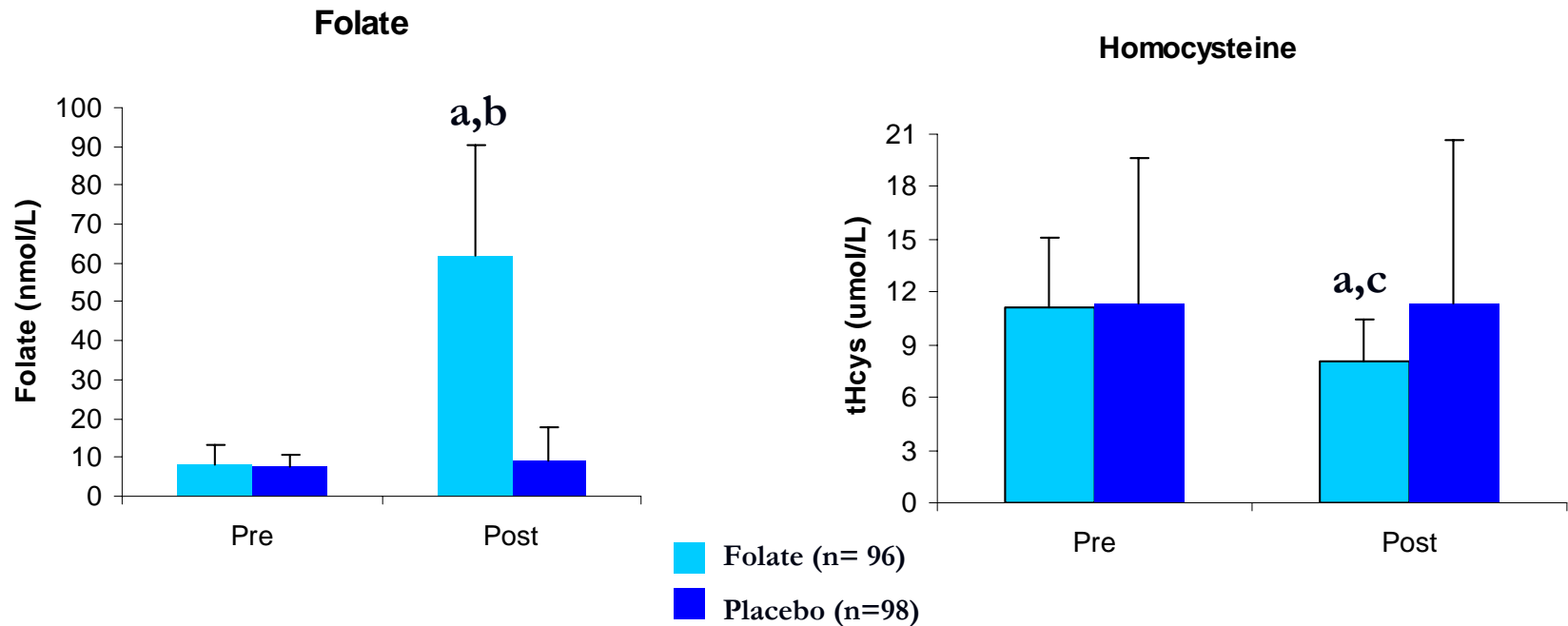
Folate supplementation to folate deficient
Bangladeshi adults enhances the
methylation of arsenic.

Study Design:

Placebo-controlled Folate Intervention Trial

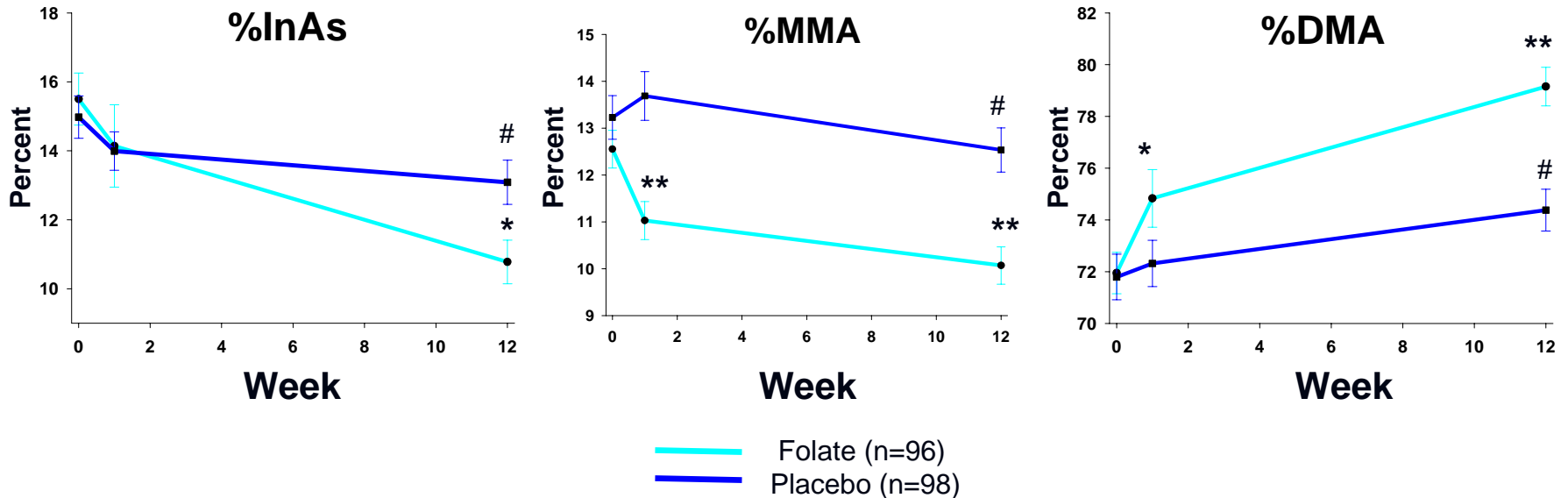
- 200 folate-deficient Bangladeshi adults
 - (Plasma folate < 9 nM)
- 12 weeks: Folic Acid (400 µg/d) or placebo
- Urinary As metabolites analyzed:
 - 0, 1, & 12 weeks
- All participants received a supply of multivitamins upon completion of the study

Results: Nutritional Parameters Pre- and Post-Intervention



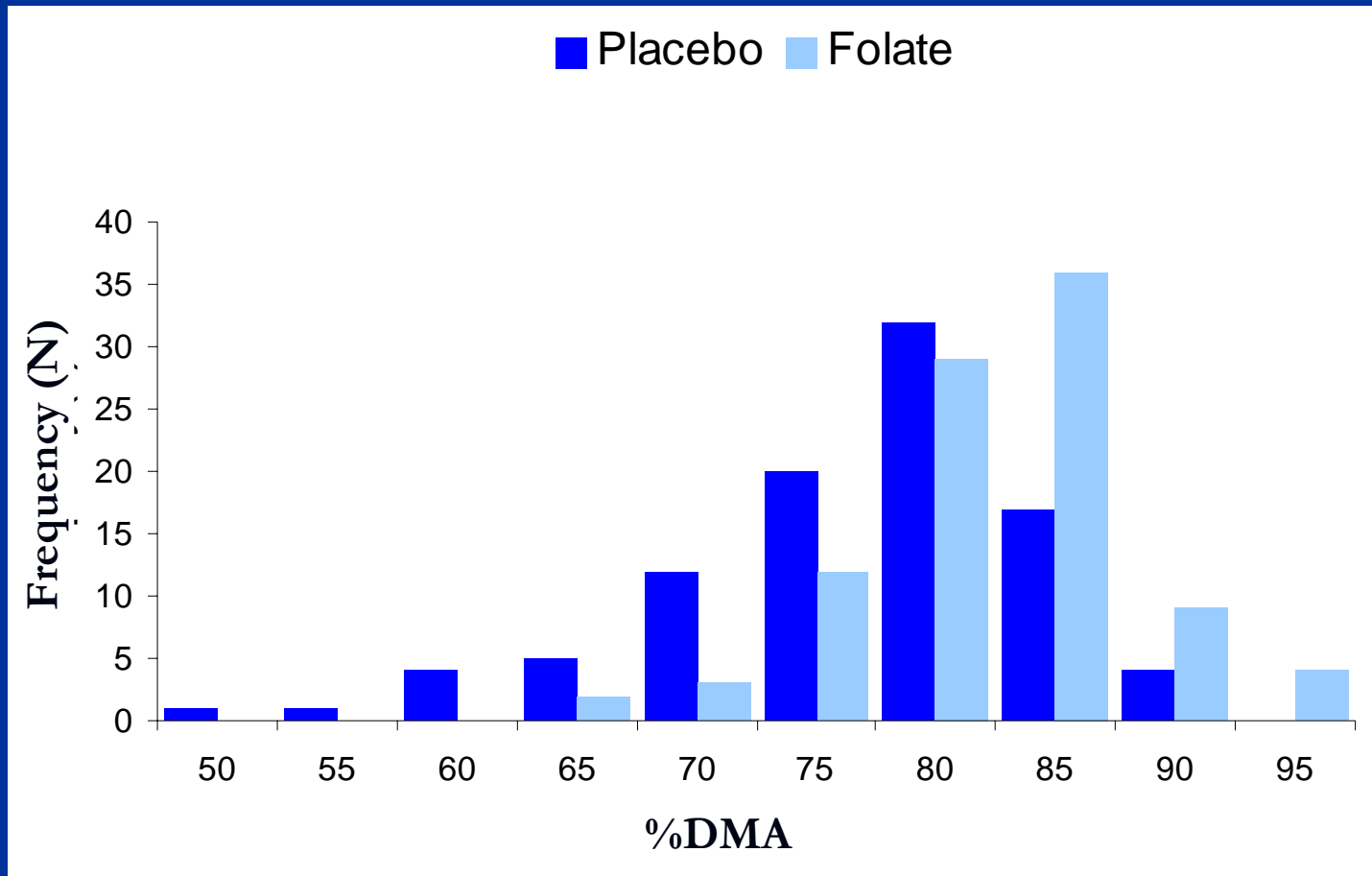
a: $p < 0.0001$ within group; b: $p < 0.0001$ between groups; c: $p < 0.001$ between groups
Wilcoxon rank sum test for continuous variables

Results: Effects of Folate Supplementation on Arsenic Metabolites in Urine



* $p < 0.05$; ** $p < 0.001$ (folate vs. placebo); # $p \leq 0.05$ (placebo pre- vs. post intervention)
Repeated measures linear regression

Distribution of %DMA in Urine after 12 Weeks Folate or Placebo Supplementation



■ Summary:

- Folate intervention study indicates a causal relationship between folate supplementation and arsenic methylation in a folate-deficient population in Bangladesh.

■ Implications:

- Enhancing arsenic methylation, as achieved by adequate folate status, could reduce arsenic-induced health outcomes.

■ Future research:

- In a nested case-control study, we will determine if folate deficiency is a risk factor for subsequent development of arsenic-induced skin lesions.

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