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

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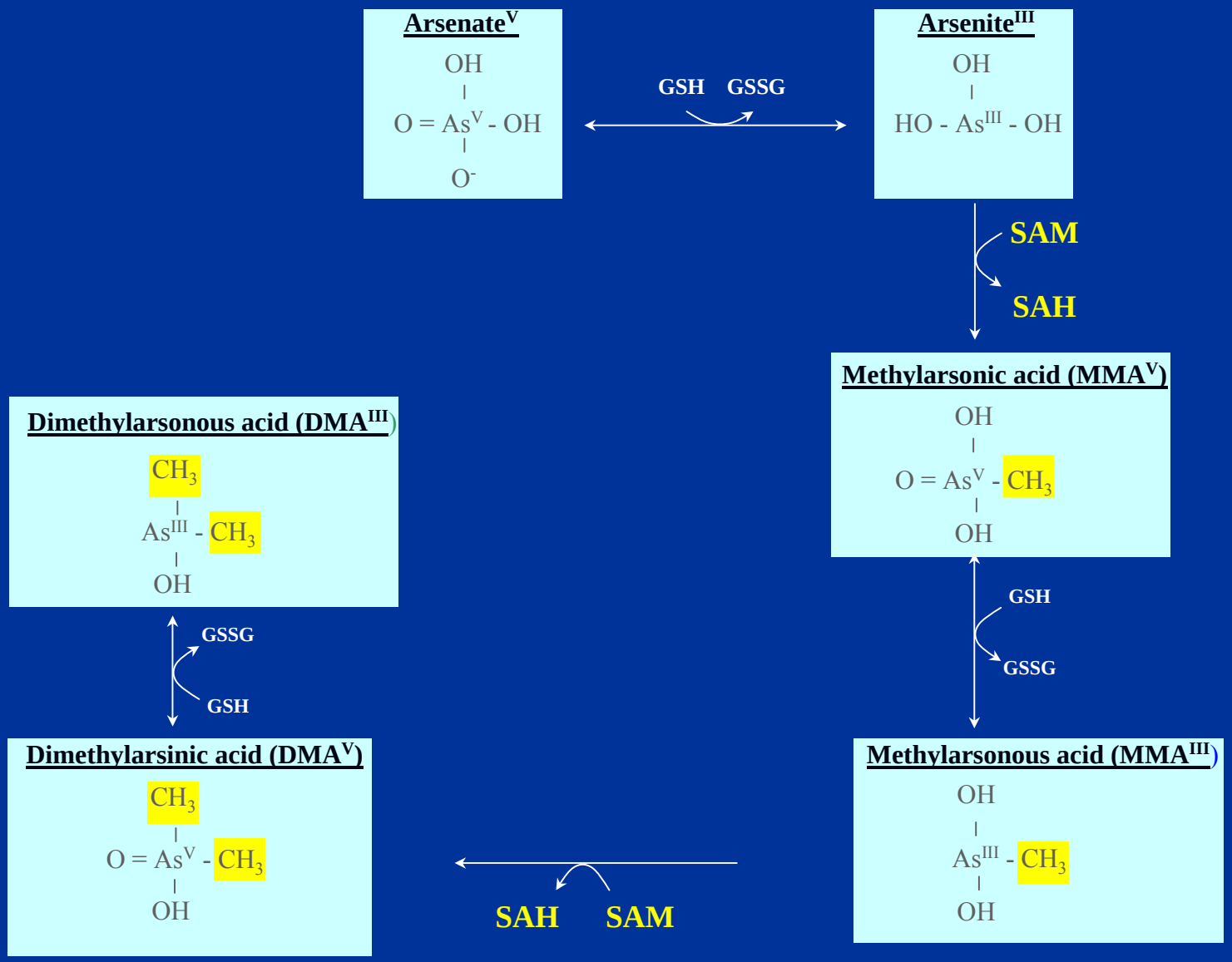
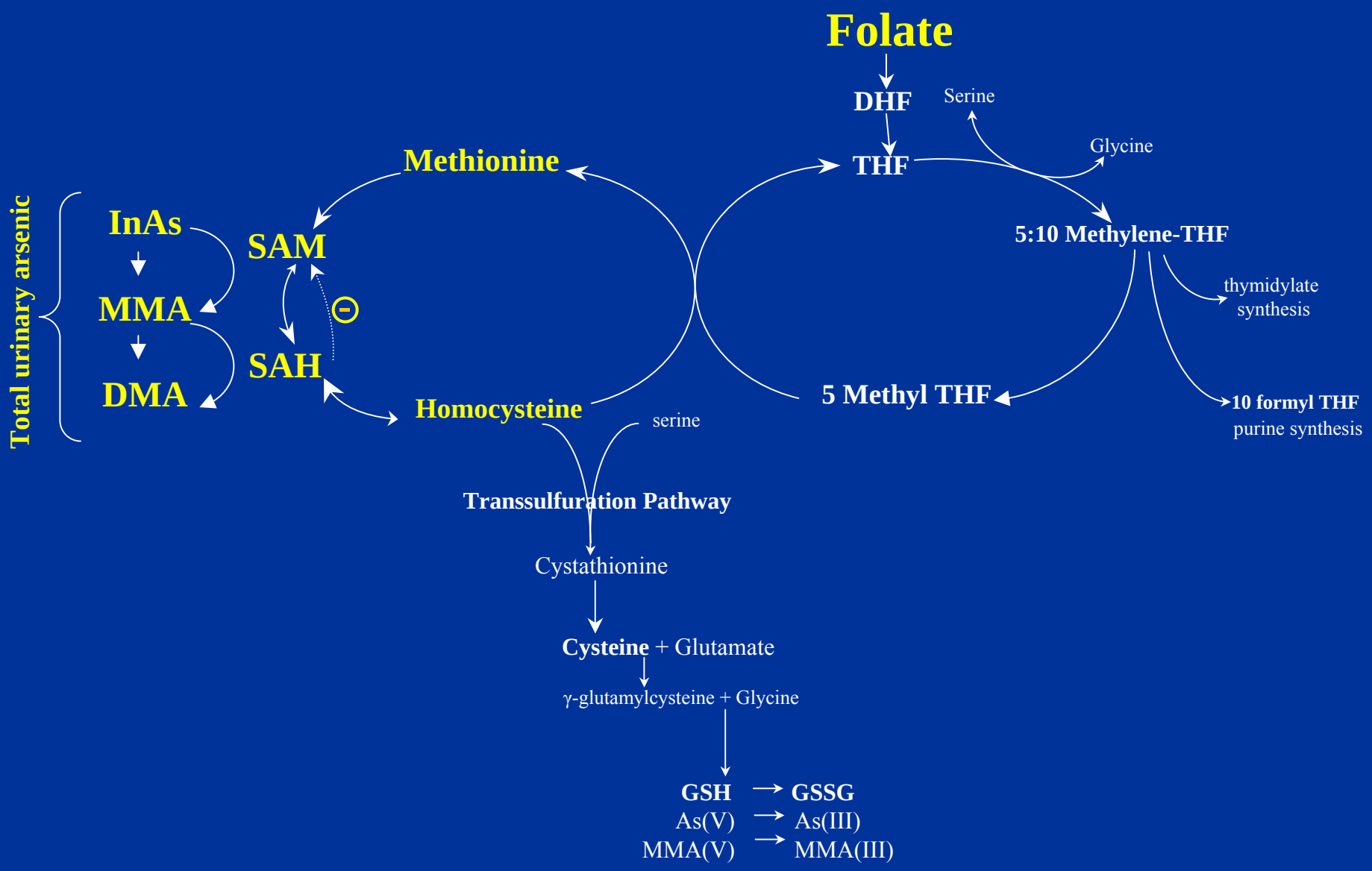
RO1 ES011601 & P42 ES10349

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 * $p < 0.05$, ** $p < 0.001$, # $p < 0.001$

Environ Health Perspect 2005, 113:1683-88

Placebo-controlled Folate Intervention Trial

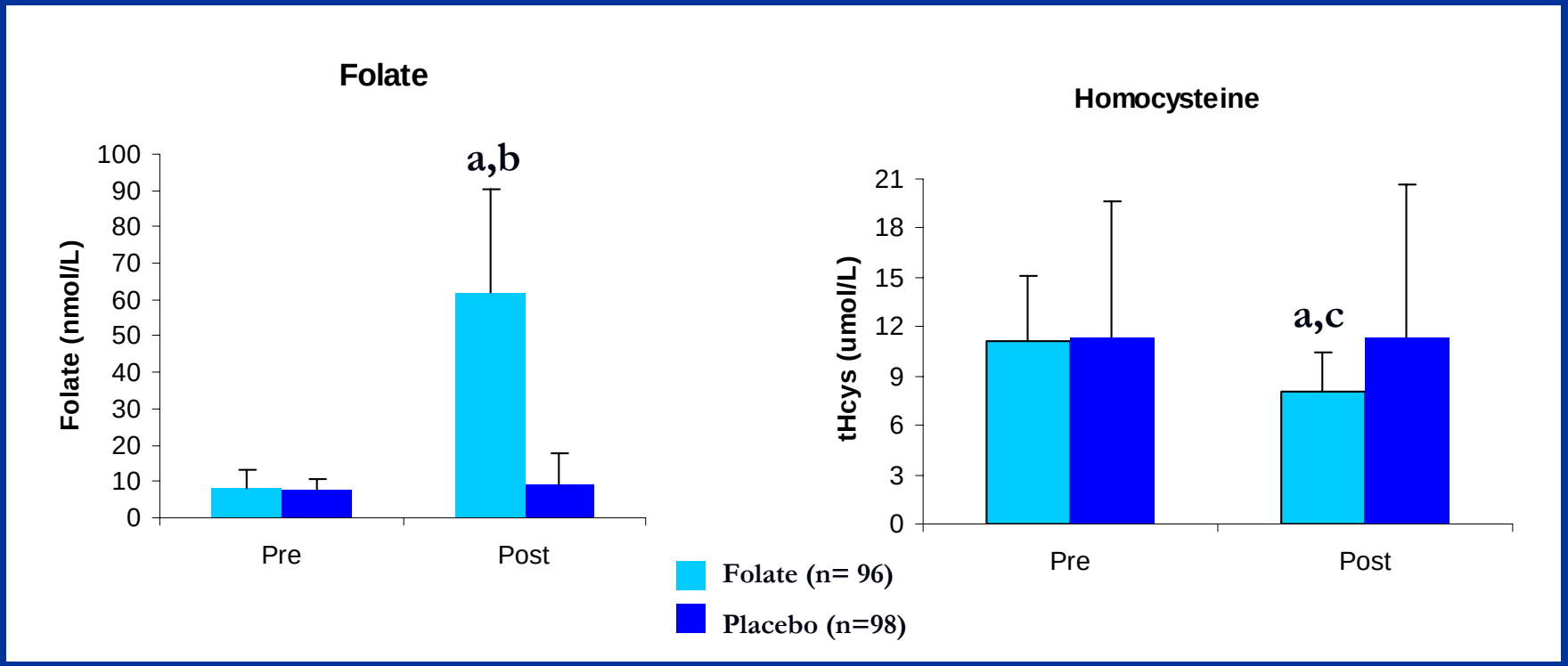
Hypothesis

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

Study Design:
Placebo-controlled Folate Intervention Trial

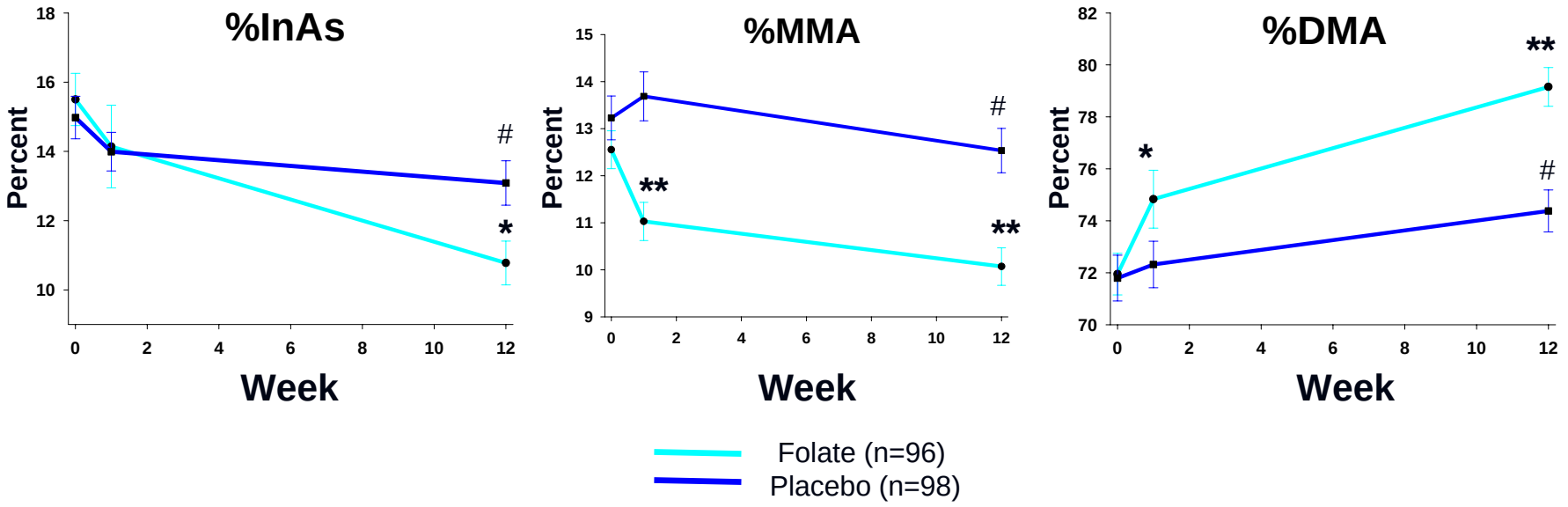
- 200 folate-deficient Bangladeshi adults
  - (Plasma folate < 9 nM)
- 12 weeks: Folic Acid (400 µg/d) or placebo
- Urinary As metabolites analyzed:
  - 0, 1, & 12 weeks
- All participants received a supply of multivitamins upon completion of the study

Results: Nutritional Parameters Pre- and Post-Intervention



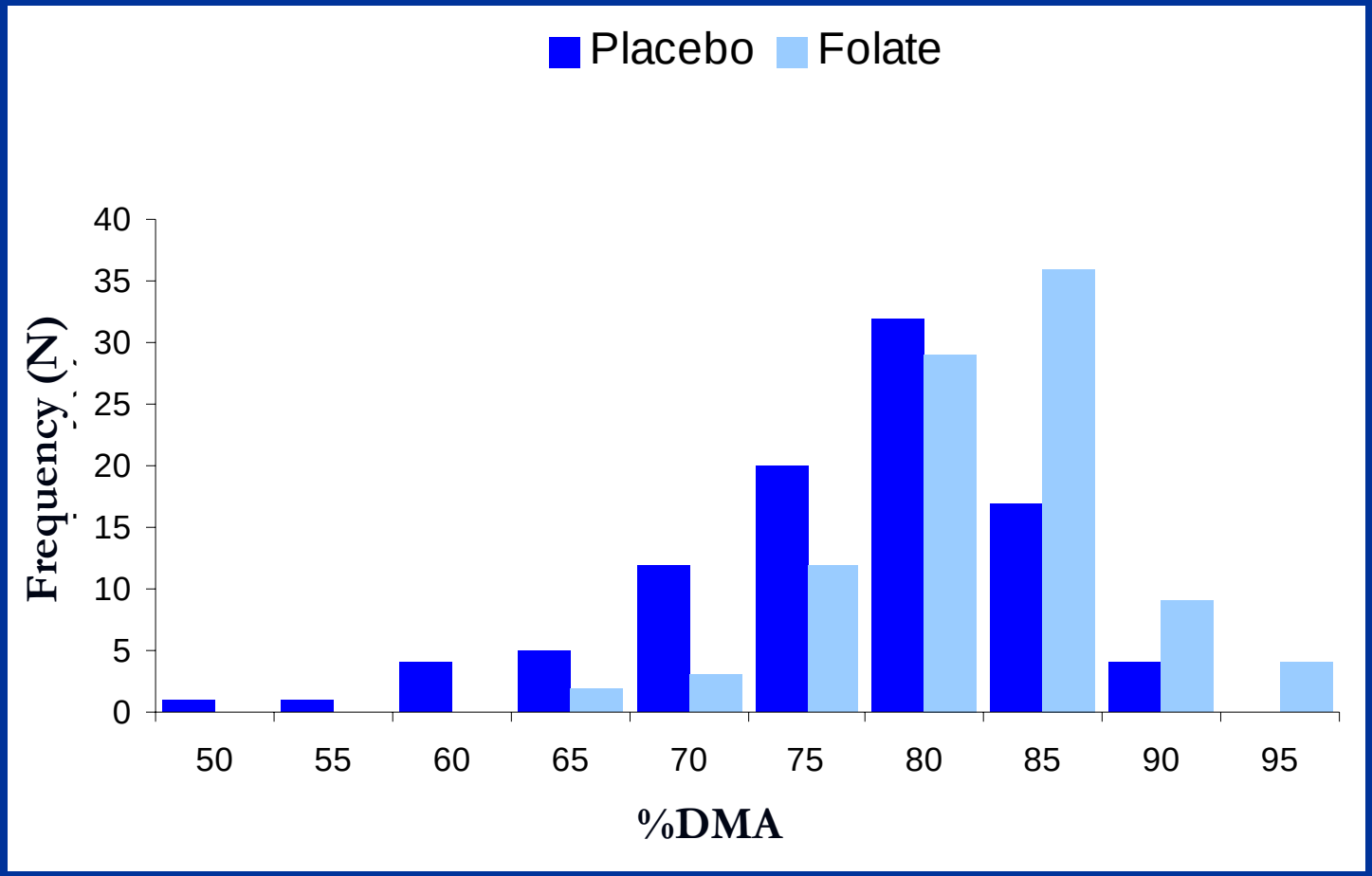
a: $p < 0.0001$ within group; b: $p < 0.0001$ between groups; c: $p < 0.001$ between groups
Wilcoxon rank sum test for continuous variables

Results: Effects of Folate Supplementation on Arsenic Metabolites in Urine



*p < 0.05; ** p < 0.001 (folate vs. placebo); # p ≤ 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-inducedhealth 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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