

Interplay Between *S*-adenosylmethionine, Folate, Cobalamin, and Arsenic Methylation in Bangladesh

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MAILMAN SCHOOL
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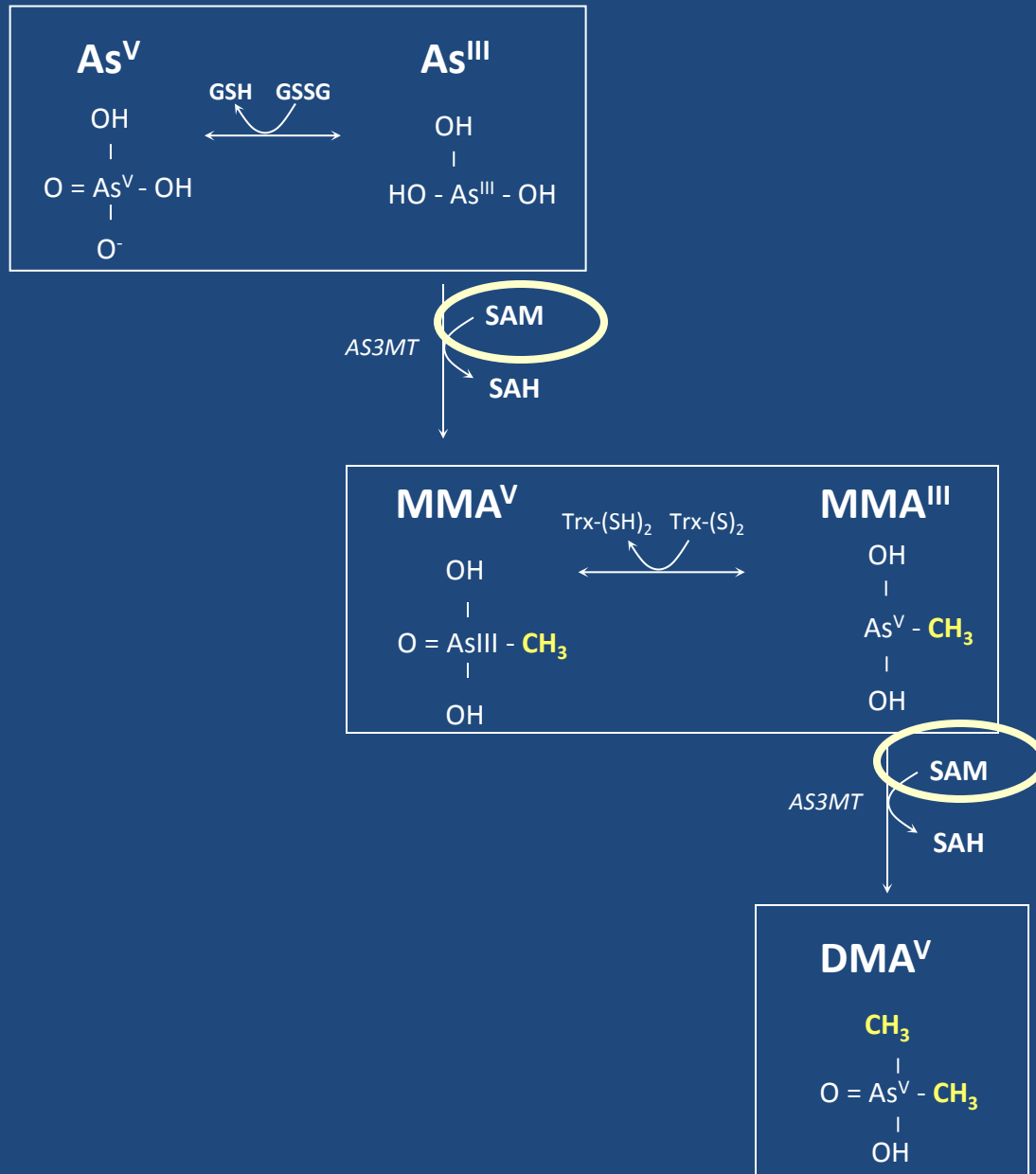
Arsenic Exposure in Bangladesh

- ~57 million people chronically exposed to water arsenic $>10\mu\text{g}/\text{L}$ (World Bank 2005)
- Chronic exposure associated with many adverse health outcomes:
 - Skin lesions
 - Skin, bladder, liver, lung, and kidney cancers
 - Ischemic heart disease and stroke
 - Neurological problems
 - Decreased pulmonary function
- Inter-individual variation in susceptibility
 - May be partially explained by differences in arsenic metabolism



<http://www.organic-center.org>

Arsenic metabolism



One-carbon metabolism

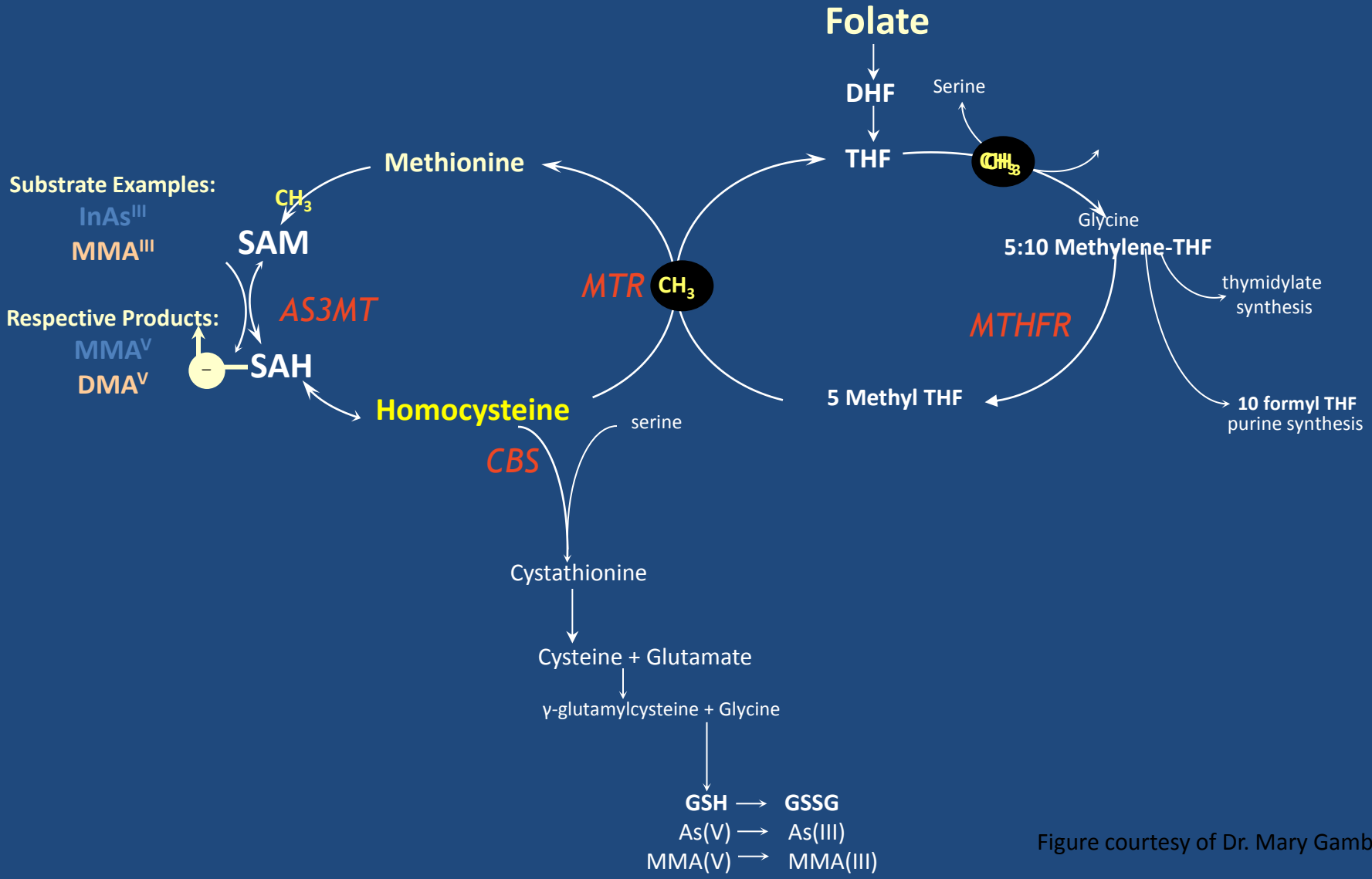


Figure courtesy of Dr. Mary Gamble

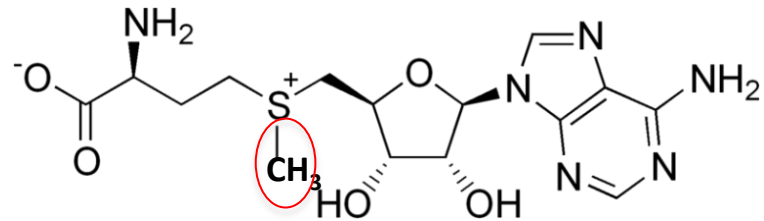
Previously observed:

High folate associated with ↓ %InAs and ↓ %MMA and ↑ %DMA

Hypothesis:

Associations between SAM and the arsenic metabolites will vary by folate and cobalamin status

S-Adenosylmethionine (SAM)

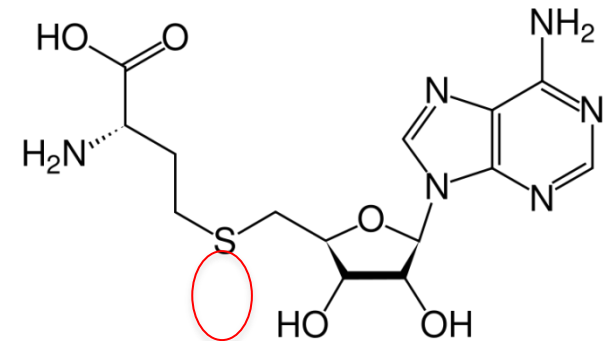


Substrate:

As^{III}

MMA^{III}

S-Adenosylhomocysteine (SAH)

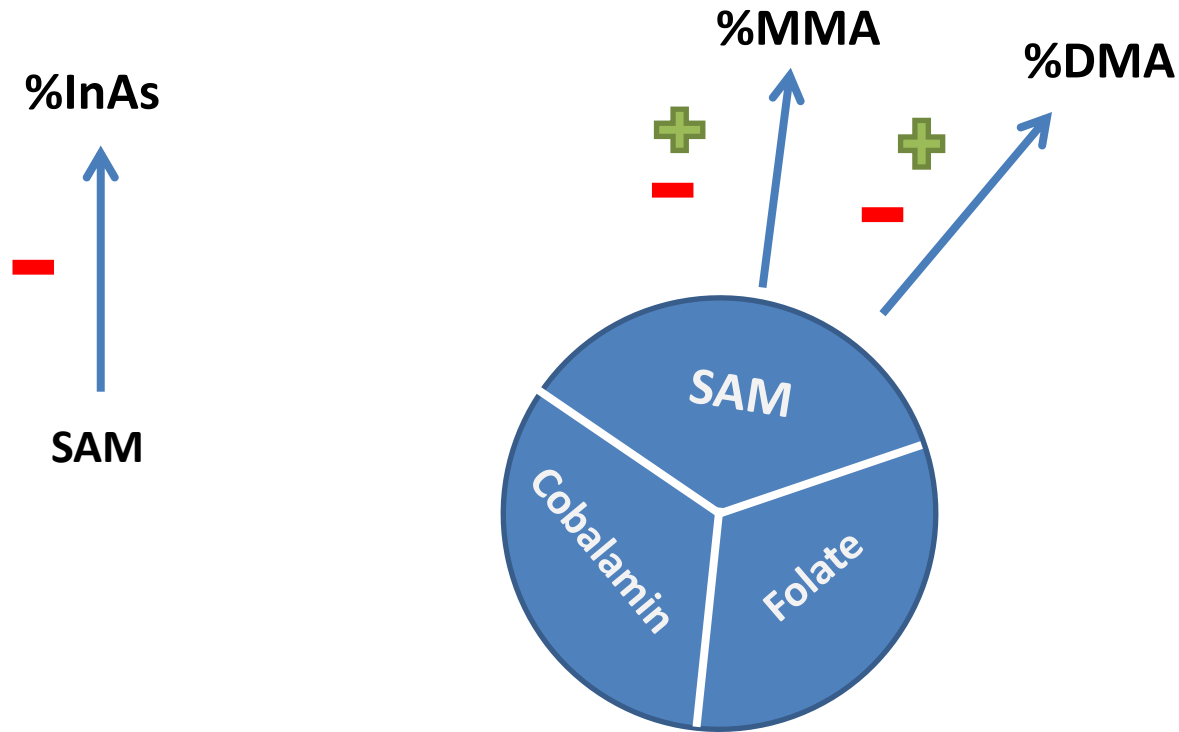


Methylated Product:

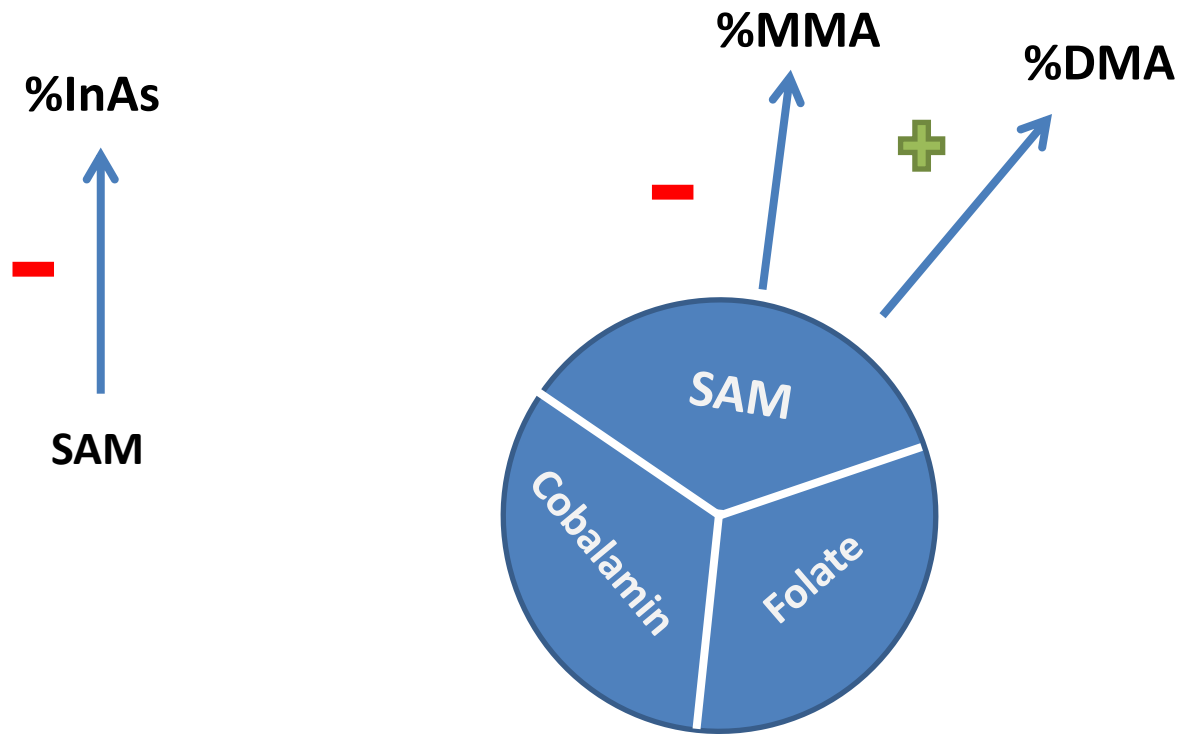
MMA^V

DMA^V

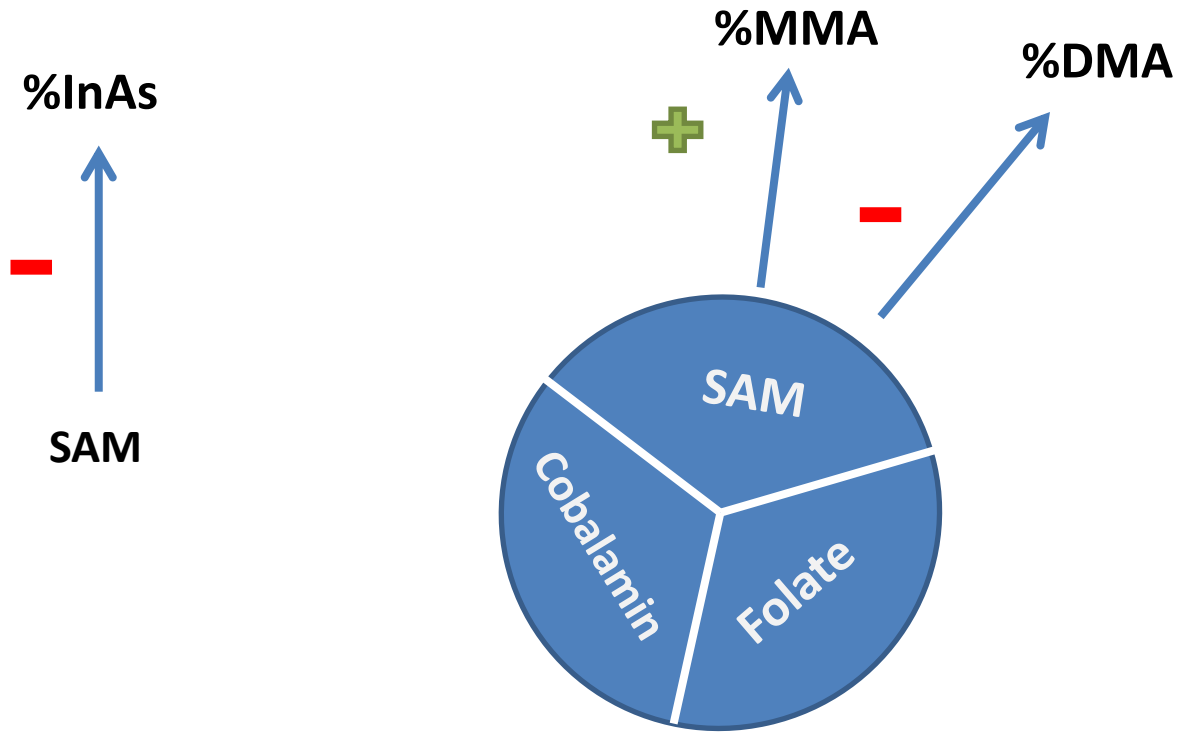
Specific Hypotheses



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Folate and Oxidative Stress (FOX) Study: Superfund, Project 4 Cross-Sectional

Planned

N = 375 (75 per category of wAs):

Group A: 0 – 10 µg/L

Group B: 10 – 100 µg/L

Group C: 100 – 200 µg/L

Group D: 200 – 300 µg/L

Group E: > 300 µg/L

Actual

N = 379

Group A: 0 – 10 µg/L (n=76)

Group B: 10 – 100 µg/L (n=104)

Group C: 100 – 200 µg/L (n=86)

Group D: 200 – 300 µg/L (n=67)

Group E: > 300 µg/L (n=45)

Descriptive Statistics

N=359	Mean \pm SD	Median (Range)
Age (yrs)	43.2 \pm 8.3	42.0 (30 – 63)
Education (yrs)	3.4 \pm 3.6	3.0 (0 – 16)
wAs ($\mu\text{g/L}$)	138.8 \pm 124.2	114 (0.37-700)
uCr (mg/dL)	54.4 \pm 43.4	40.3 (4.3 – 223.5)
Ever smoker (%)		36.4
TV ownership (%)		58.1
Sex (% female)		50.0
BMI < 18.5 (%)		33.3
Folate Deficient <9 nmol/L (%)		29.6
Cobalamin Deficient <151 pmol/L (%)		36.6

Spearman Correlations Folate and Arsenic Metabolites

	FOX						NIAT		
	<u>Blood Metabolites (N=295)</u>			<u>Urinary Metabolites (N=359)</u>			<u>Urinary Metabolites (N=295)</u>		
	%InAs	%MMA	%DMA	%InAs	%MMA	%DMA	%InAs	%MMA	%DMA
Folate	-0.12*	-0.21#	0.27##	-0.13**	-0.20##	0.23##	-0.12*	-0.08	0.12*

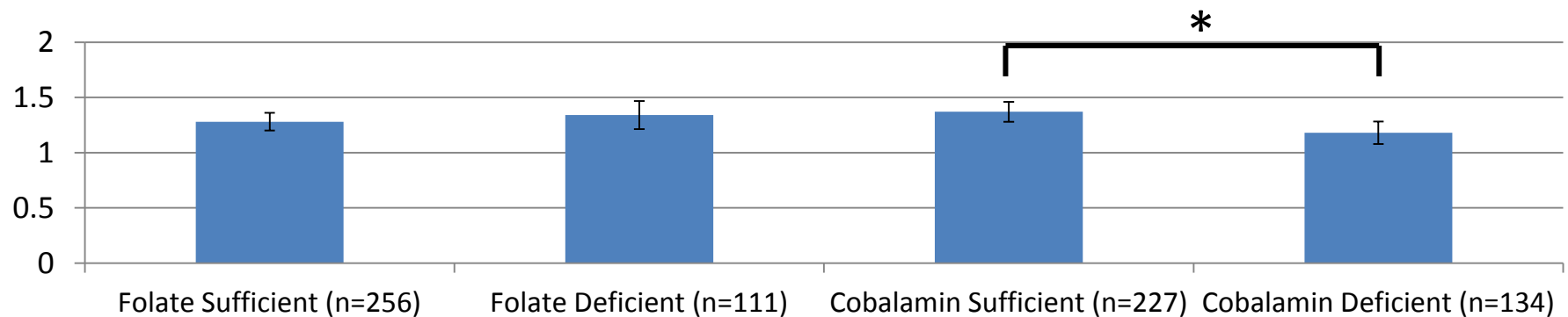
*p<0.05, **p<0.01, #p<0.001, ##p<0.0001

Folate, Cobalamin, and SAM

Spearman Correlations with SAM (N=359)

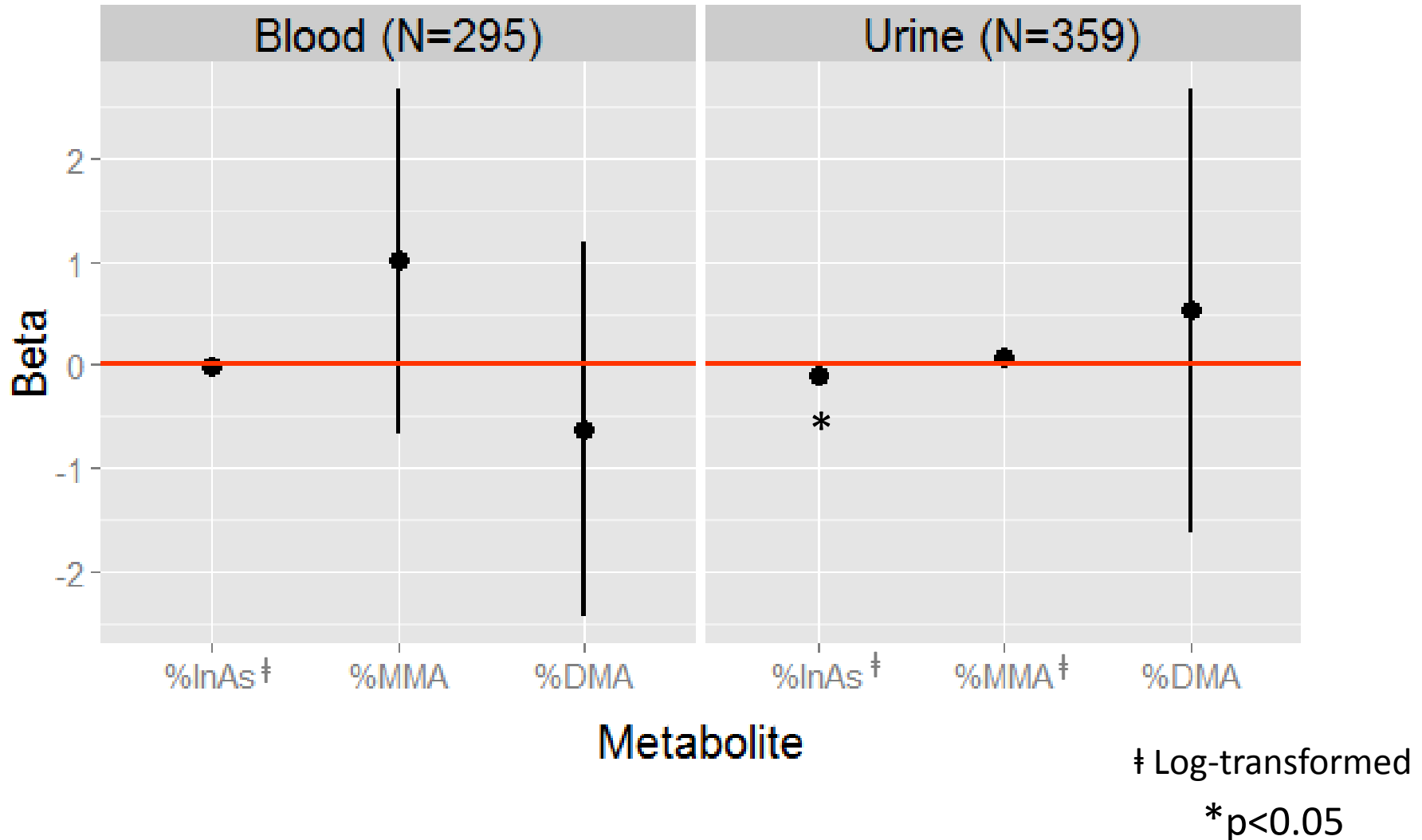
	Rho	P-value
Folate	-0.069	0.192
Cobalamin	0.182	<0.001

Mean SAM levels by Folate and Cobalamin Status



* p-value < 0.05

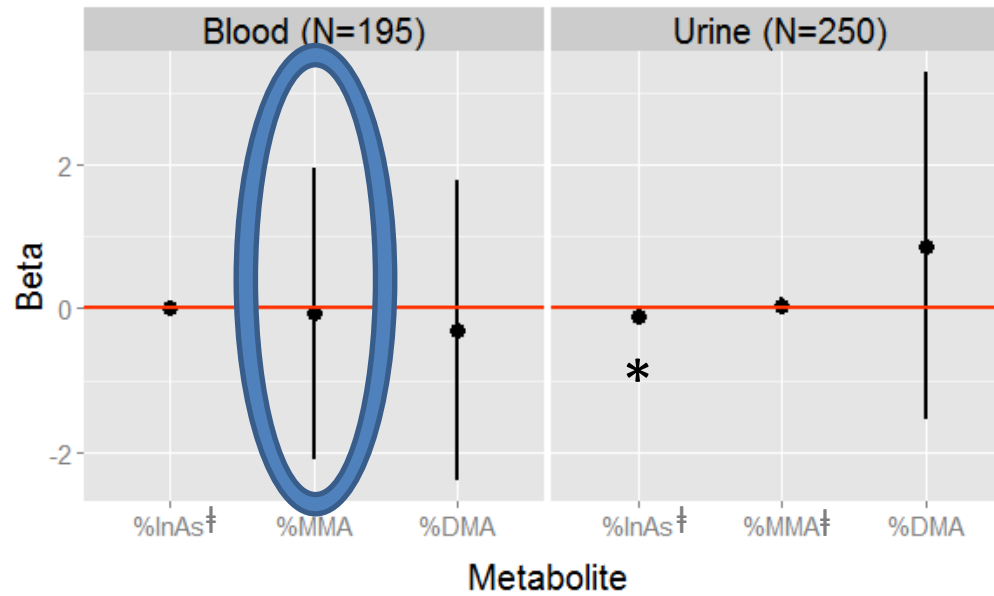
Associations Between SAM and %Metabolite



All models adjusted for sex, cigarette smoking, total water arsenic exposure, and age

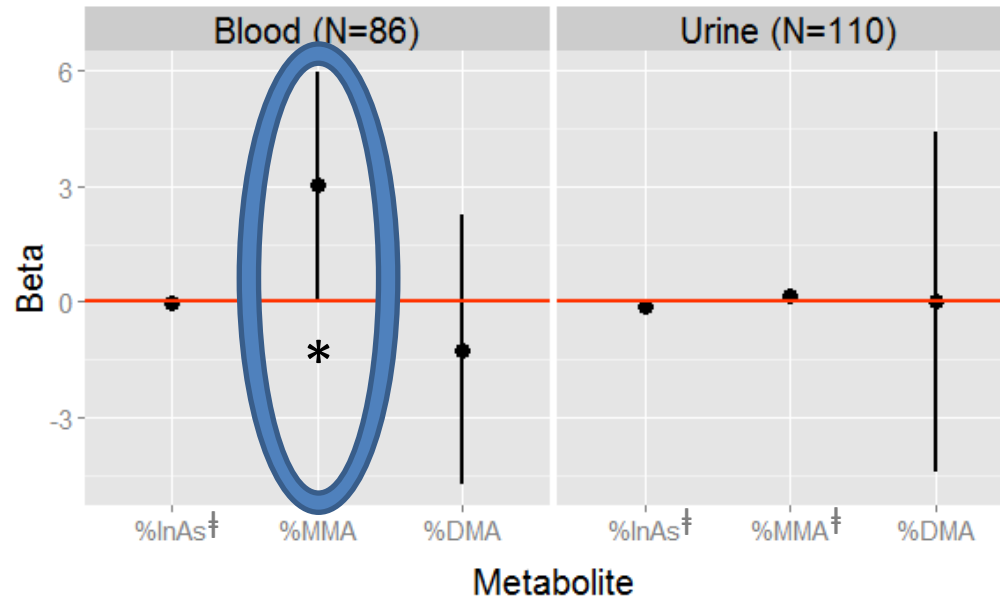
Associations Between SAM and %Metabolite, by Folate Status

Folate Sufficient



*p<0.05

Folate Deficient

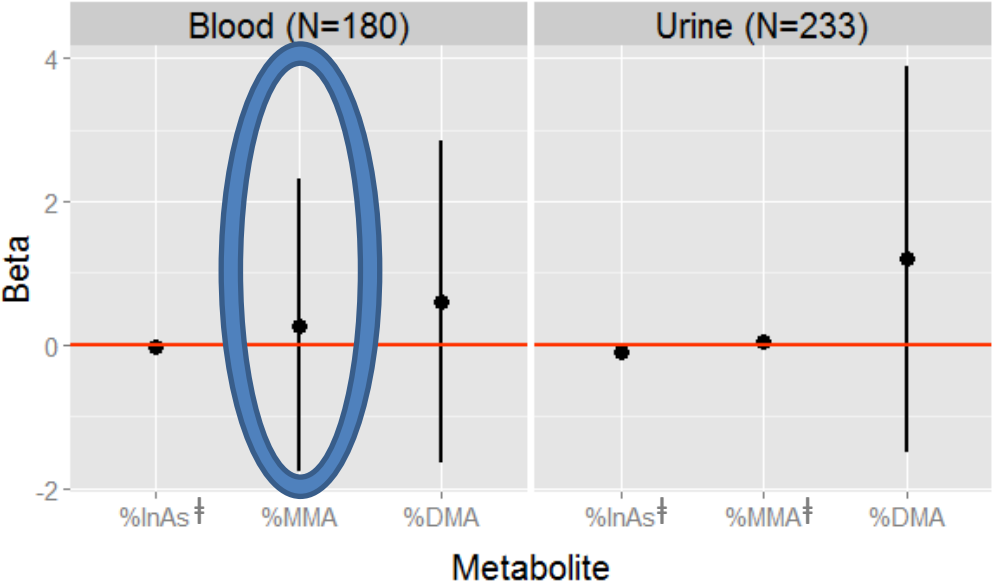


p-value=0.01 for SAM*folate with respect to %bMMA

All models adjusted for sex, cigarette smoking, total water arsenic exposure, and age

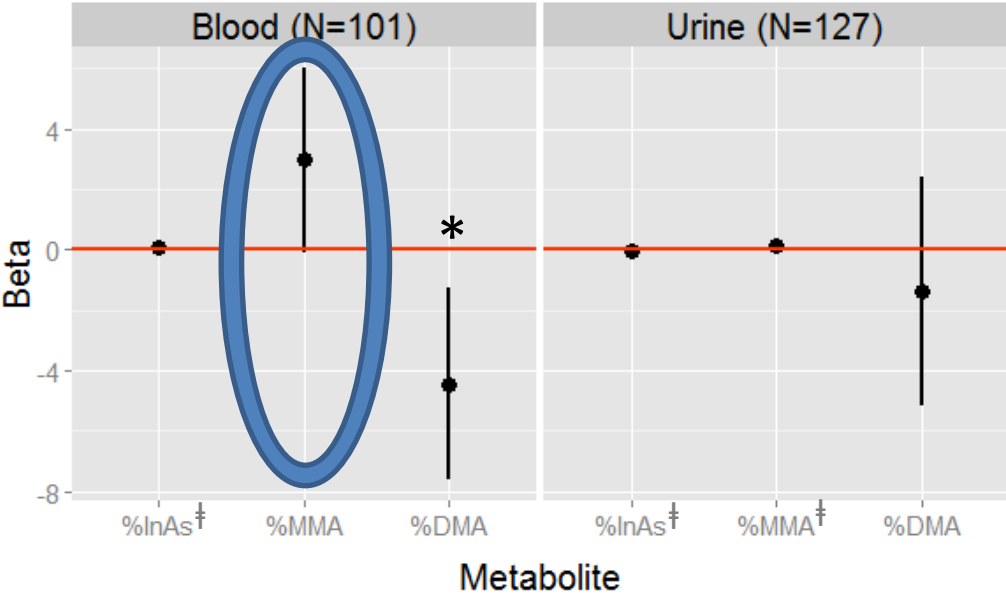
Associations between SAM and %Metabolite, by Cobalamin Status

Cobalamin Sufficient



*p<0.05

Cobalamin Deficient

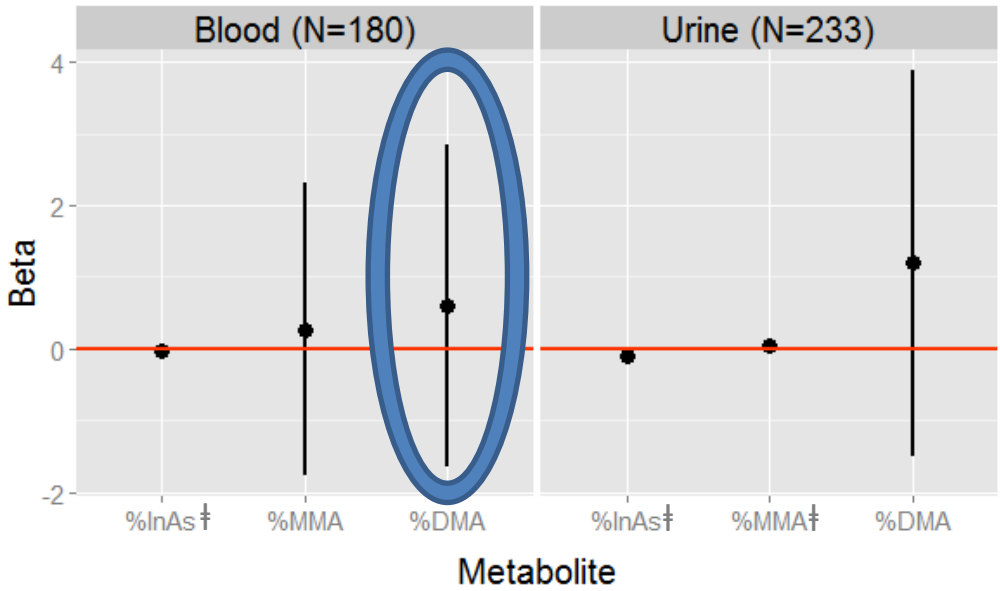


p-value =0.07 for SAM*cobalamin with respect to %bMMA

All models adjusted for sex, cigarette smoking, total water arsenic exposure, and age

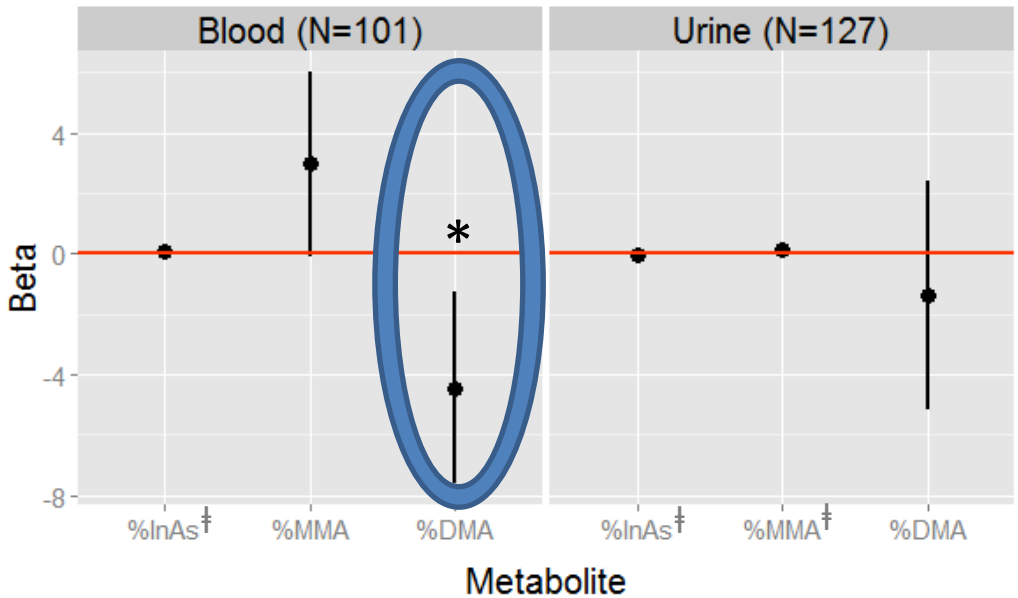
Associations between SAM and %Metabolite, by Cobalamin Status

Cobalamin Sufficient



*p<0.05

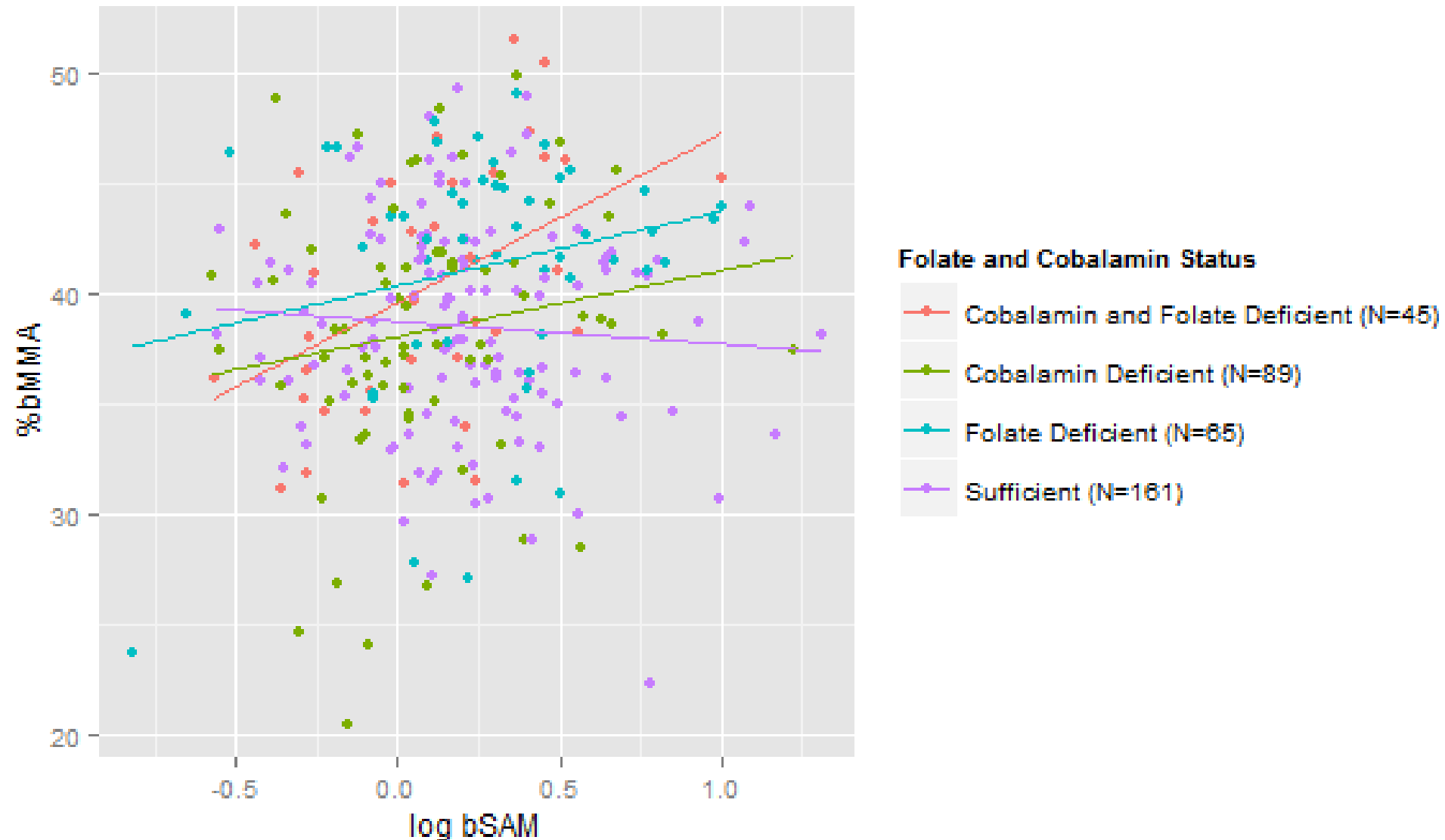
Cobalamin Deficient



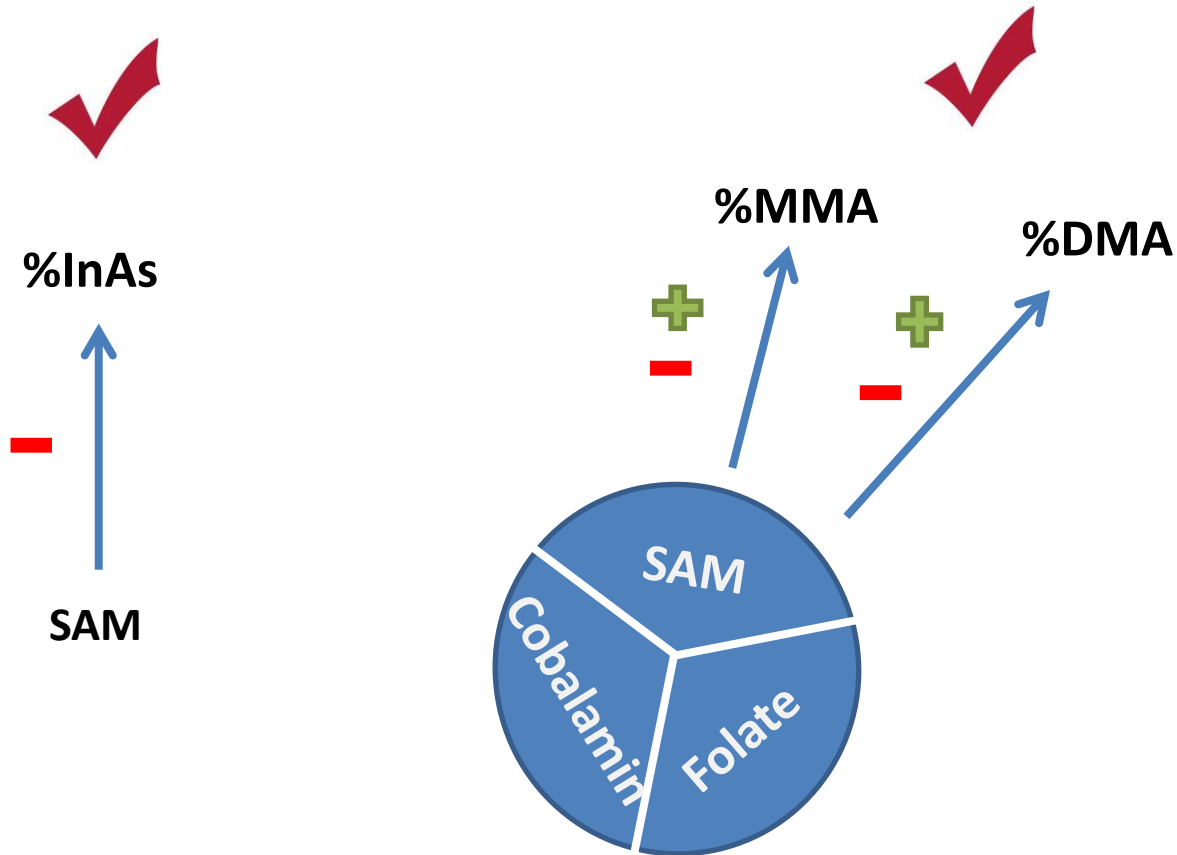
p-value =0.01 for SAM*cobalamin with respect to %bDMA

All models adjusted for sex, cigarette smoking, total water arsenic exposure, and age

SAM and %bMMA by Folate *and* Cobalamin Status



Summary



Conclusions

Take-away message:

- When folate or cobalamin levels low, SAM associated with higher %MMA

Public health implications

- Individuals with B vitamin deficiencies may be at increased risk of As-induced toxicity

Acknowledgements

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