

Slides for Discussion of Issue 2: Risk of Bias



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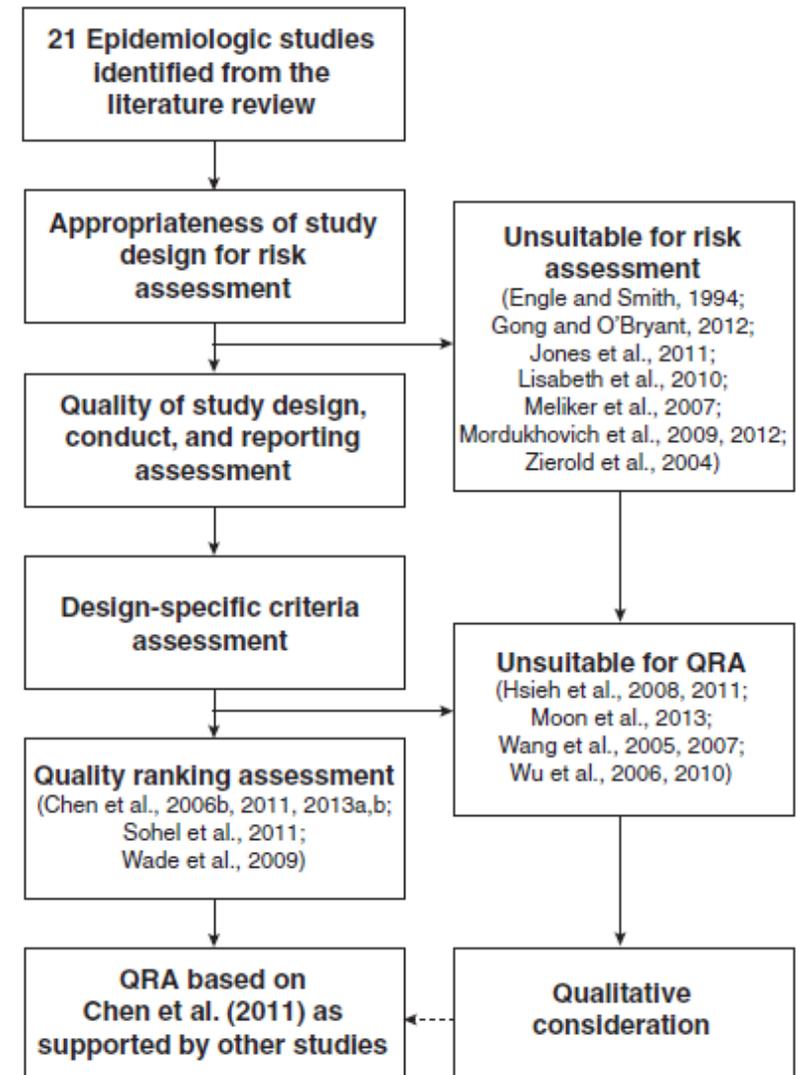
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Systematic Review and Evaluation for Risk Assessment (RA)

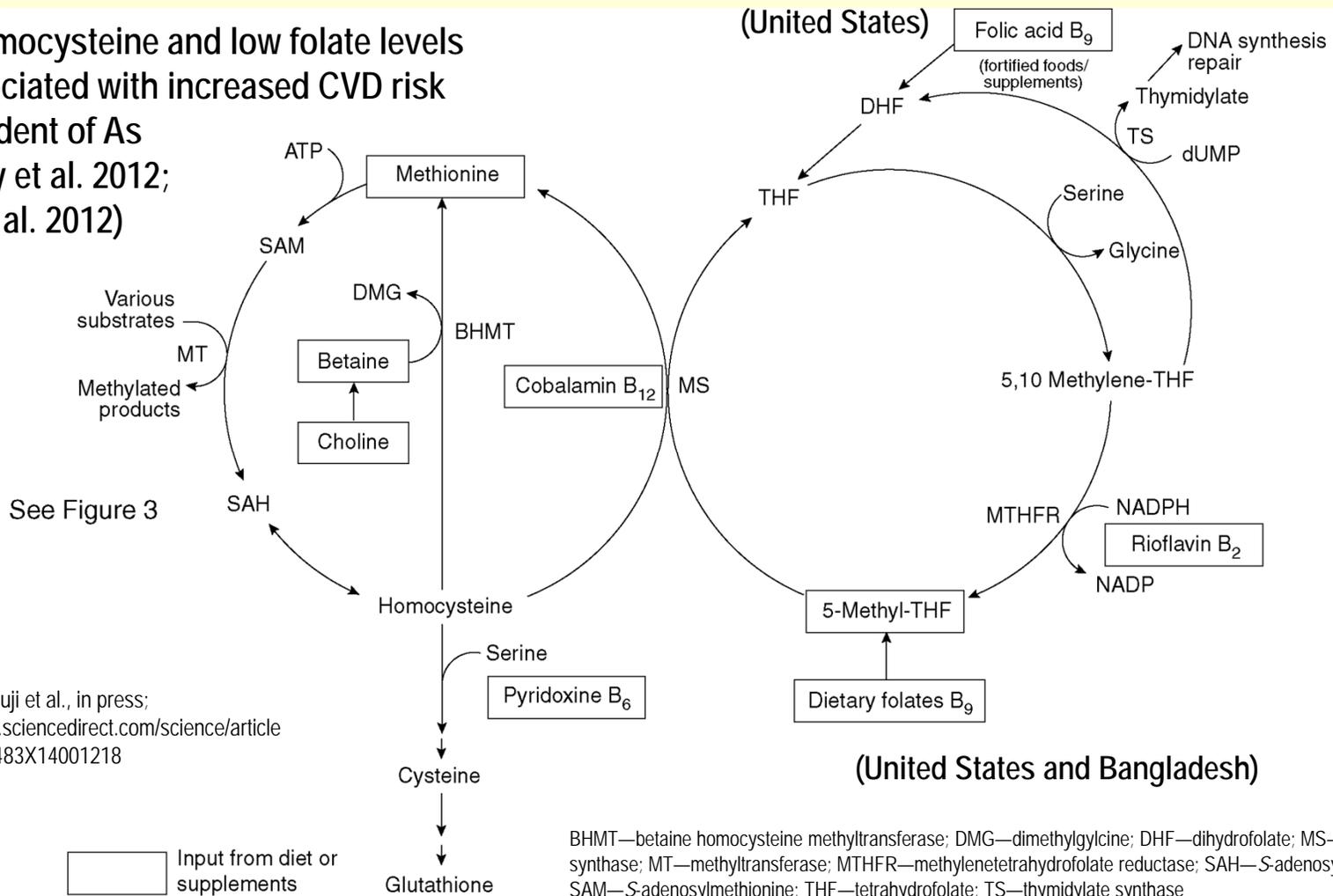
- Criteria for RA: Dose metric, risk estimate, low-level exposure
- Study Design: Case-control or cohort more powerful than cross-sectional or ecological
- Analysis: evaluation of confounders/effect modifiers/mediators
- Quality assessment: participation/attrition rate, exposure specific to iAs, outcome assessment, length of follow-up, completeness & transparency of analysis
- Evaluation of the overall evidence regarding dose-response, including review/analysis articles





Confounders and Effect Modifiers: Nutrients in One-Carbon Metabolism and Health Outcomes

High homocysteine and low folate levels are associated with increased CVD risk independent of As (McNulty et al. 2012; Wang et al. 2012)



Source: Tsuji et al., in press;
<http://www.sciencedirect.com/science/article/pii/S0300483X14001218>

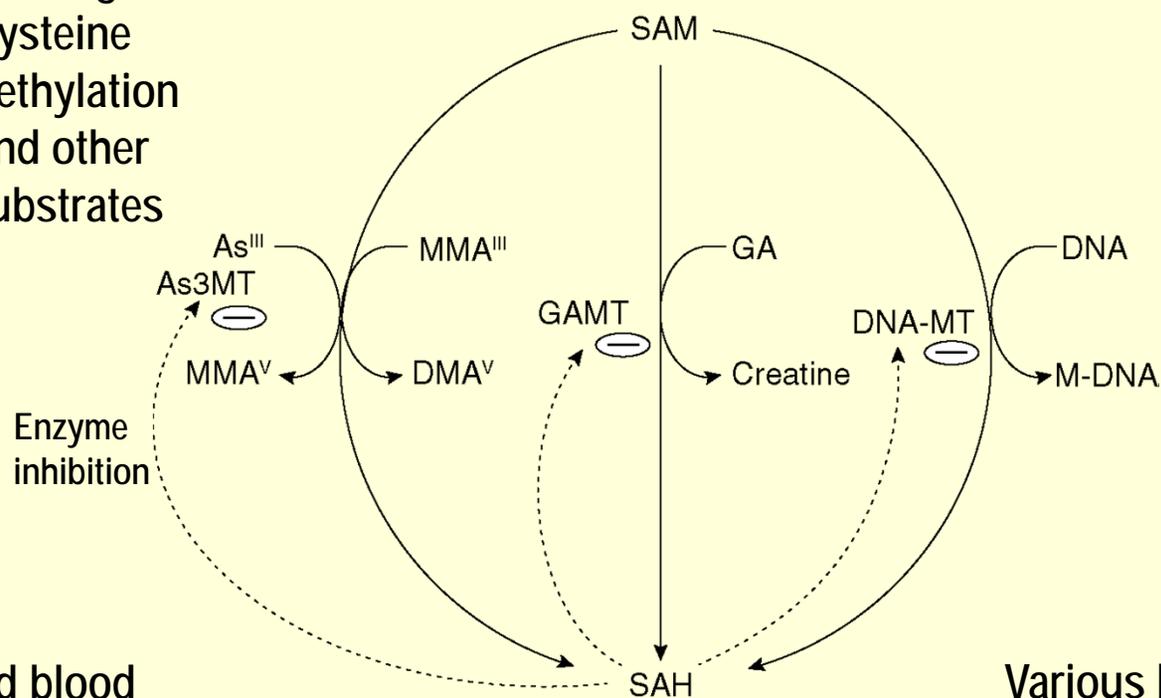
Input from diet or supplements

BHMT—betaine homocysteine methyltransferase; DMG—dimethylglycine; DHF—dihydrofolate; MS—methionine synthase; MT—methyltransferase; MTHFR—methylenetetrahydrofolate reductase; SAH—S-adenosylhomocysteine; SAM—S-adenosylmethionine; THF—tetrahydrofolate; TS—thymidylate synthase



Effect of Homocysteine on 1) Methylation of Arsenic and Other Substrates, 2) Disease Risk

Low folate and high SAH/homocysteine suppress methylation of arsenic and other important substrates



Increased blood levels of total As, iAs, MMA

Bias in apparent association

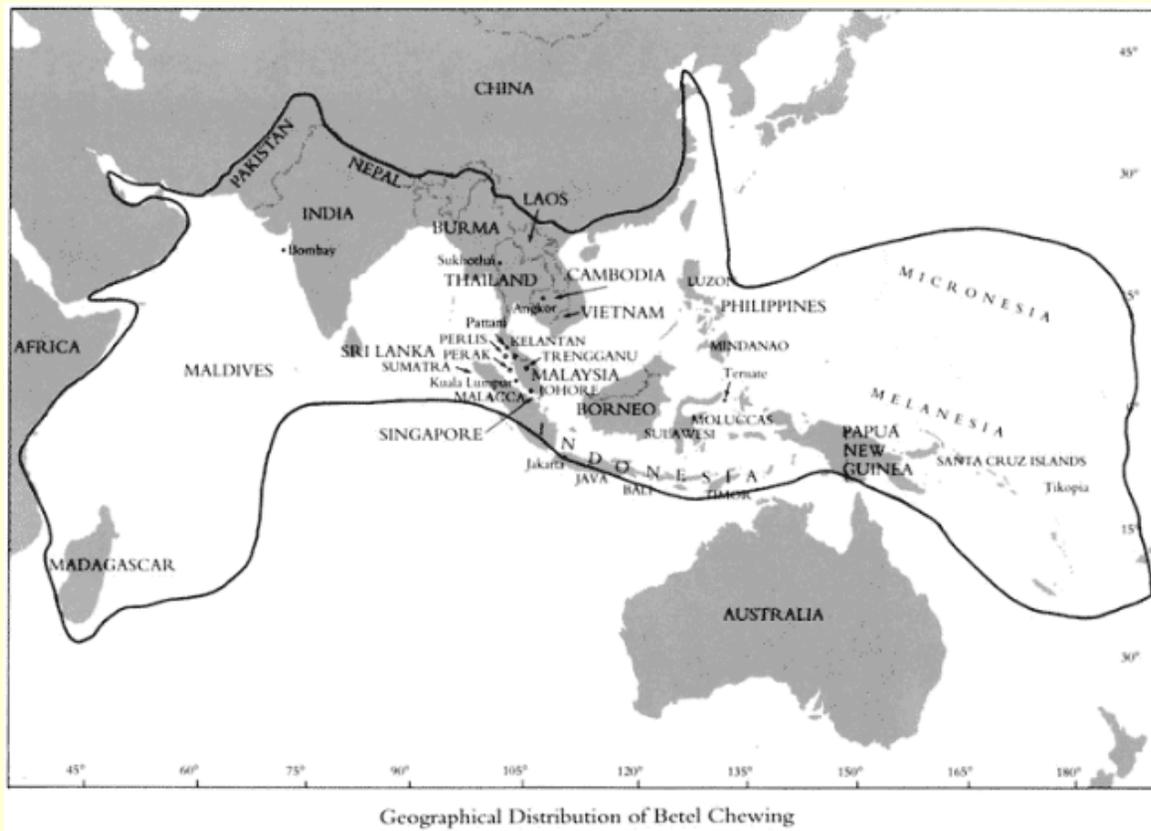
Various health effects may result from reduced methylation, *independent of As*

As^{III}—trivalent inorganic arsenic; As3MT—arsenite methyltransferase; DMA^V—pentavalent dimethylarsinic acid; DNA MT—DNA methyltransferase; GA—guanidinoacetate; GAMT—guanidinoacetate methyltransferase; MMA—monomethylarsonic acid; SAH—S-adenosylhomocysteine; SAM--S-adenosylmethionine

Source: Figure 3 in Tsuji et al., in press; <http://www.sciencedirect.com/science/article/pii/S0300483X14001218>



Geographic Distribution of Betel (Areca) Nut Use (e.g., Bangladesh, India, Taiwan)

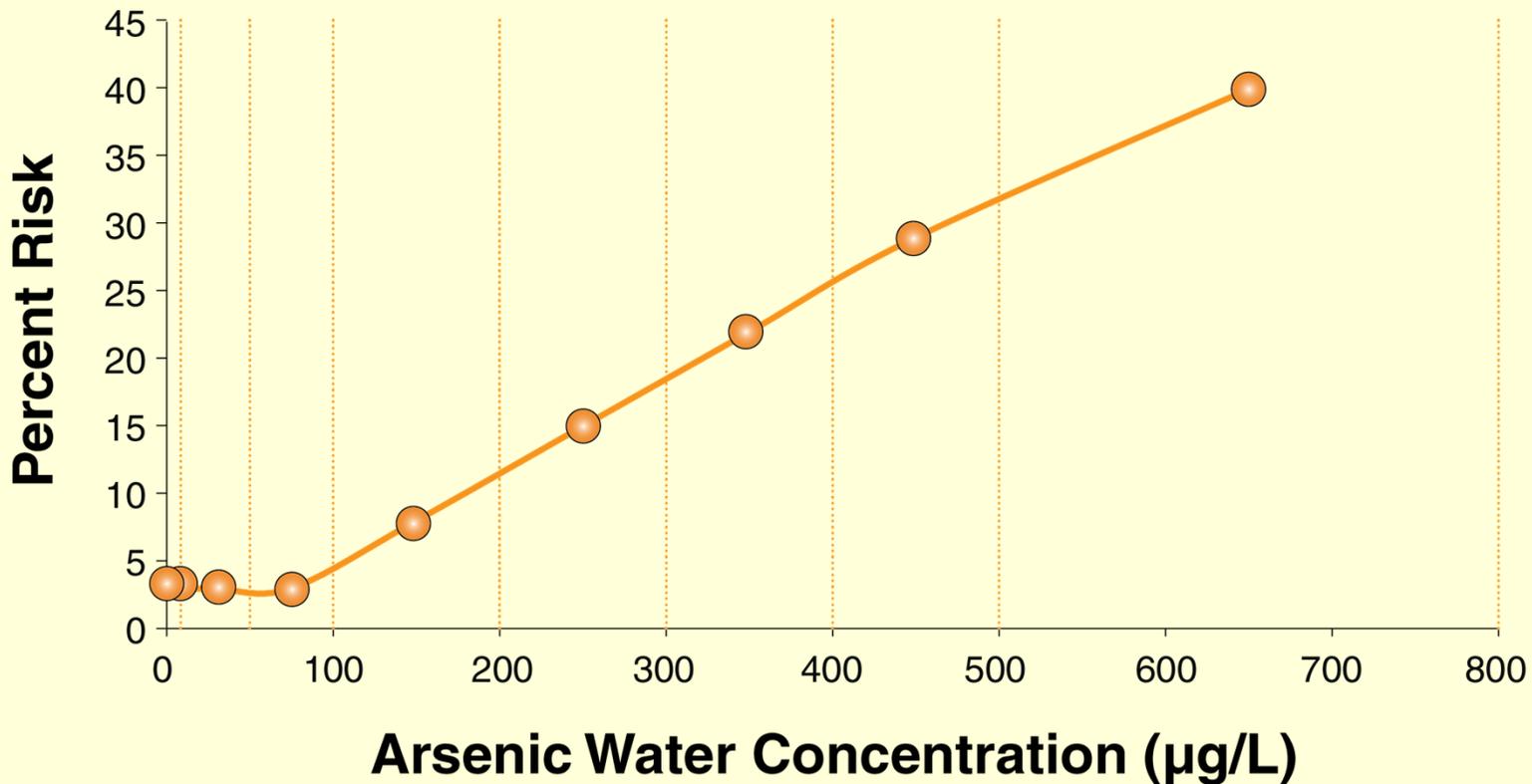


- Reduces folate status
- Increases risk of skin lesions (Pilsner et al. 2009)
- Various health risks (heart/respiratory disease, diabetes, reproductive effects, cancer (Islam and Majumder 2013; McClintock et al. 2014; WHO 2012))
- Synergistic effect with smoking
- Enhances apparent association of arsenic with these diseases

Source: Rooney (1993),
http://rooneyarchive.net/lectures/lec_betel_chewing_in_south-east_asia.htm



Effect of Dose Range within Exposure Groups on Dose-Response: Narrow Dose Ranges





Effect of Dose Range within Exposure Groups on Dose-Response: Broad Dose Ranges

