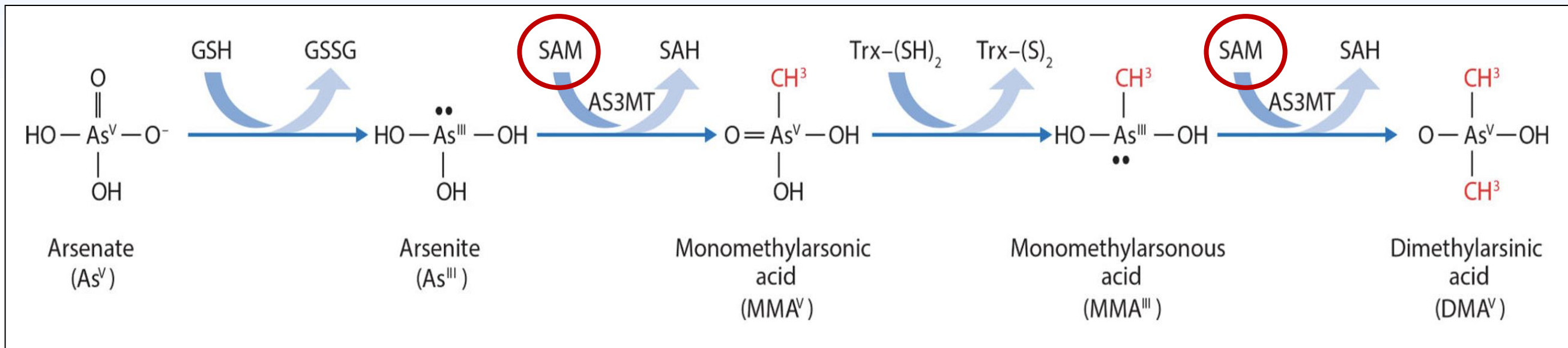


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## Background and Aims

### Background:

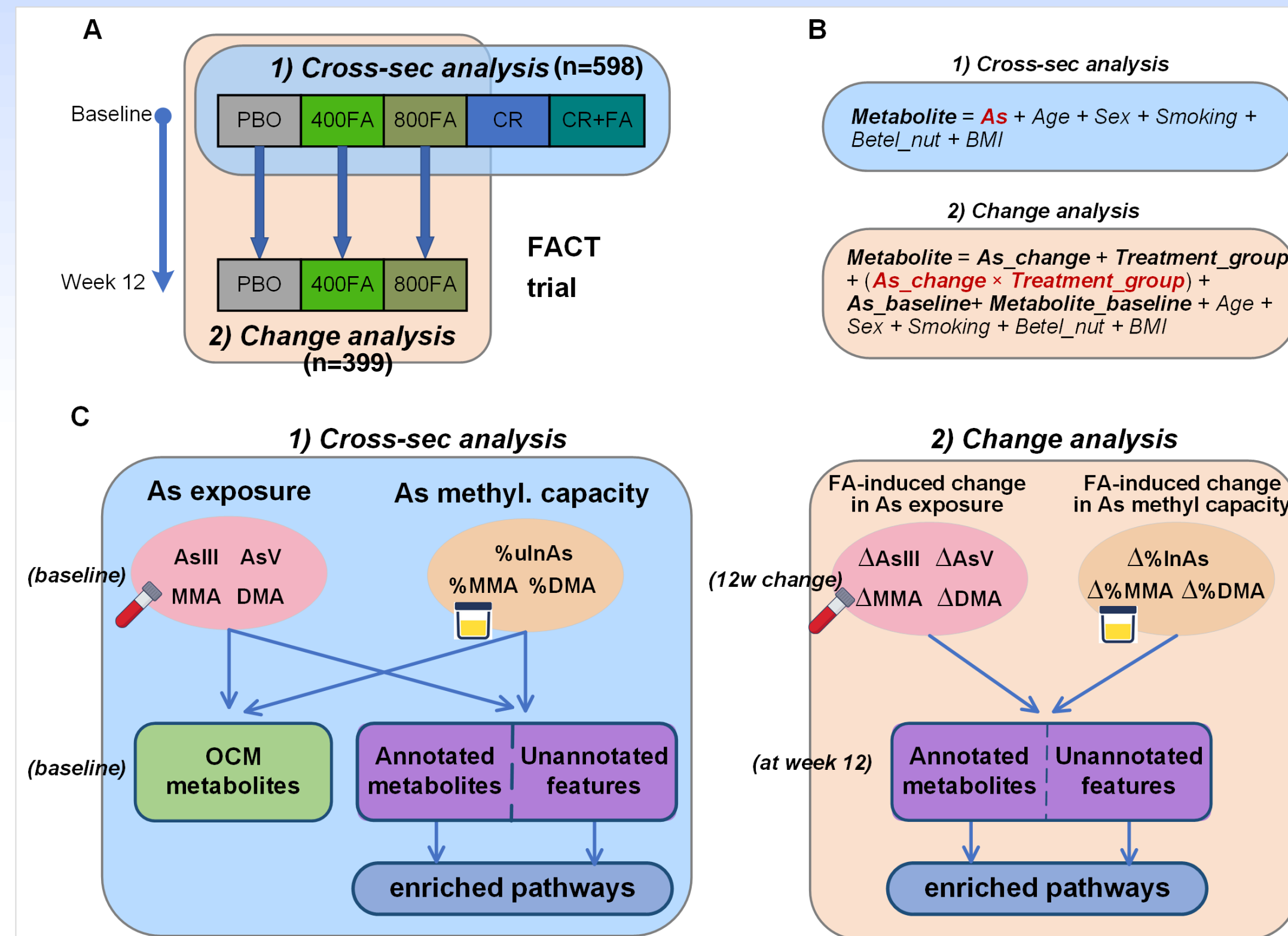
- **Arsenic** in drinking water is a leading public health concern.
- **Folic acid (FA)** influences **one carbon metabolism (OCM)**, which facilitates arsenic metabolism and excretion.



### Aims:

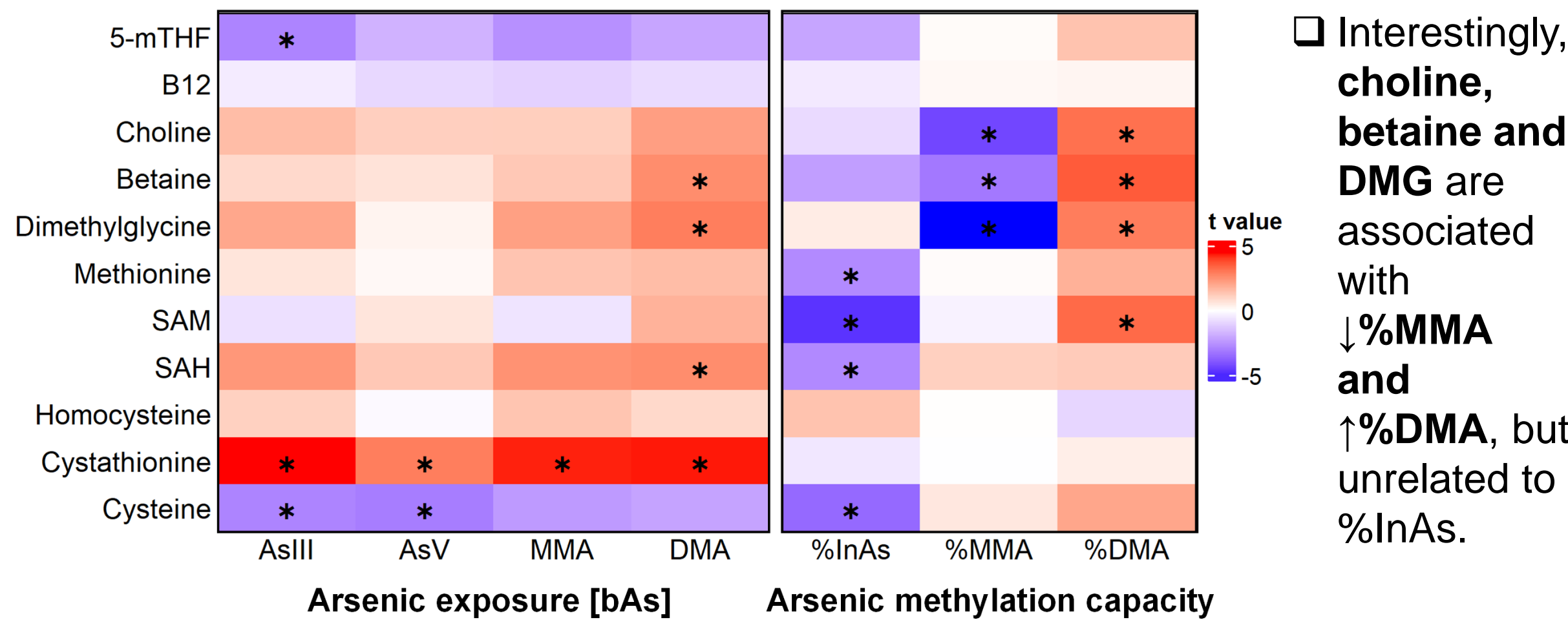
- To identify **OCM metabolites** associated with bAs or %uAs.
- To identify **metabolomic profiles** associated with bAs or %uAs, and their change induced by 12-week FA supplementation.

## Methods



## Results

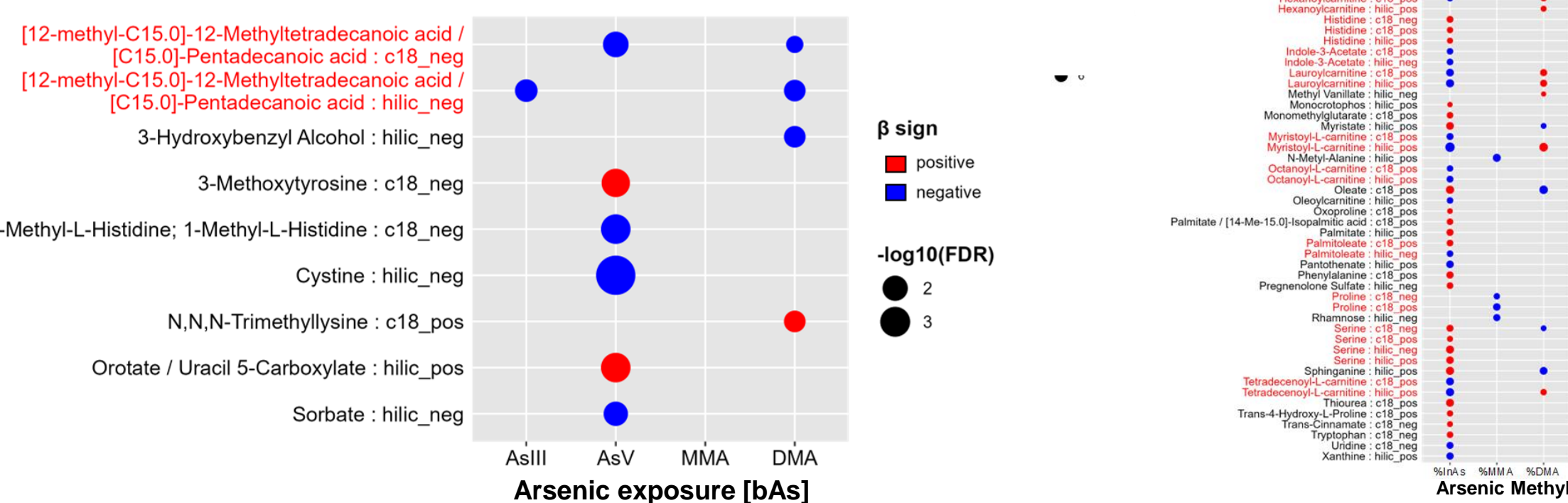
### A. OCM metabolites and arsenic at baseline (n=595)



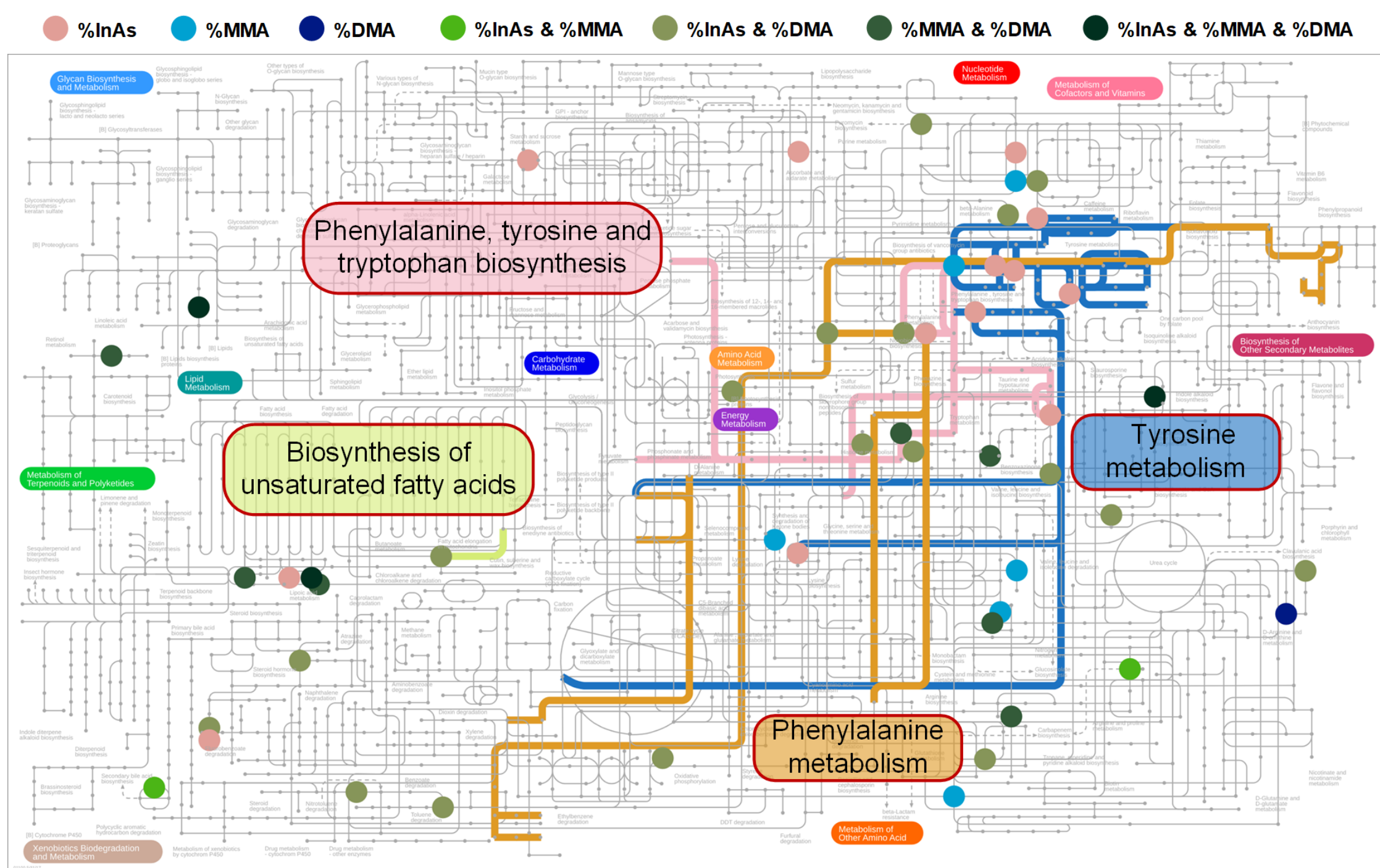
- ❑ Interestingly, **choline, betaine and DMG** are associated with **↓%MMA and ↑%DMA**, but unrelated to %InAs.
- ❑ Cystathionine may be elevated with arsenic exposure due to arsenic-induced oxidative stress and/or due to known arsenic interactions with sulfhydryl groups.

### B. metabolomic signature of arsenic

- ❑ fewer metabolites were identified for **As exposure (9)** than for **As methyl. indices (86)**.
- ❑ inorganic As were associated with more metabolites than methylated As.

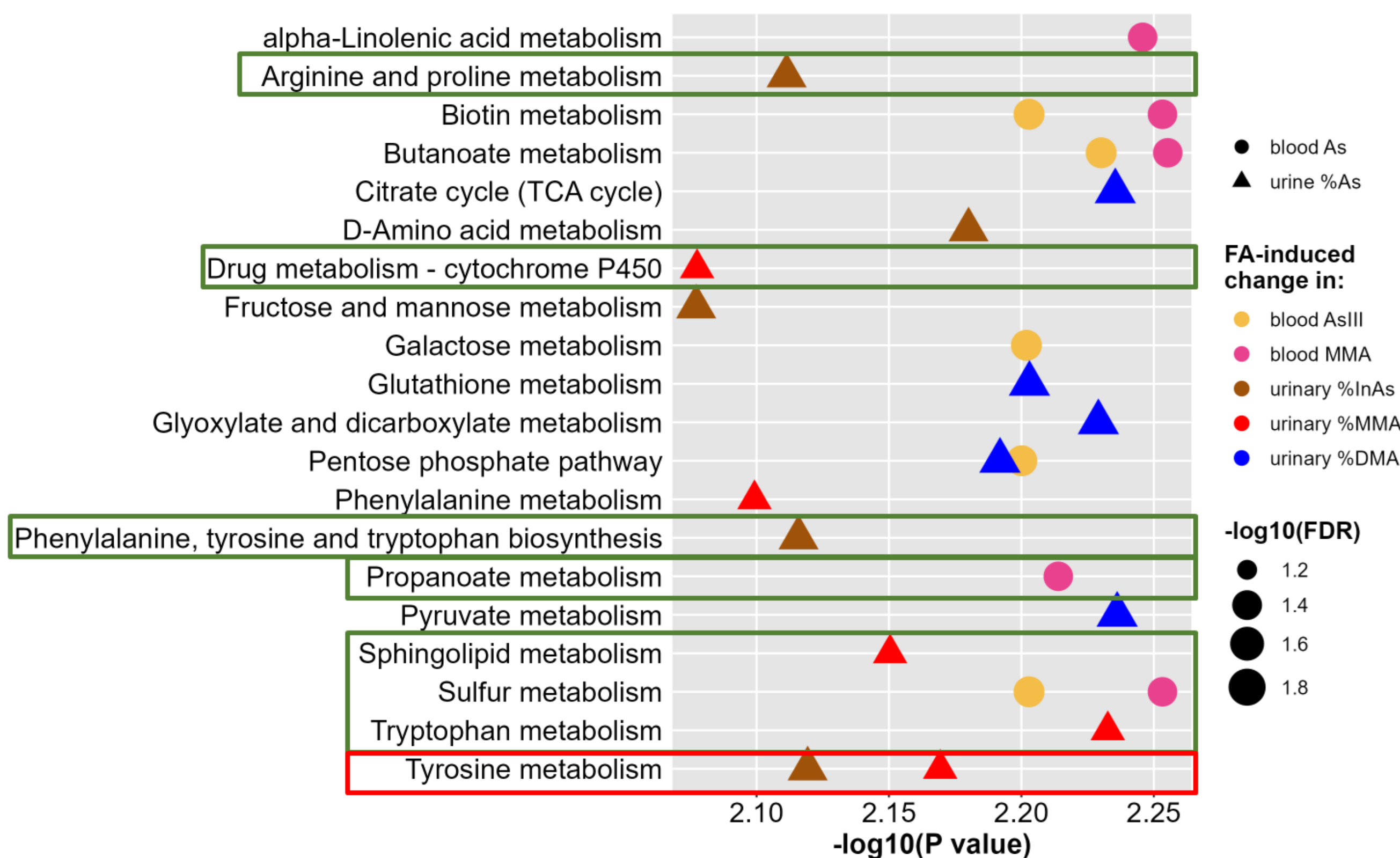


### C. Pathways for arsenic-related metabolome



- ❑ **Phenylalanine, tyrosine and tryptophan-related pathways were identified for both arsenic exposure and metabolism markers**, in both metabolite- and metabolomic feature-oriented analyses.
- ❑ Phenylalanine and tyrosine are precursors for melanin and catecholamines. **Melanosis** (skin hyperpigmentation due to increased melanin) is a hallmark of chronic arsenic exposure.

### D. metabolomic signature of FA-induced arsenic change



- ❑ For both blood and urinary arsenic, most (>94%) significant hits were found with **inorganic arsenic (bAsV and %uInAs)**, with findings consistent across two FA doses.
- ❑ Enrichment analysis highlighted the **tyrosine metabolism** pathway, with 8 pathways overlapping with cross-sectional results.

## Conclusions

- ❑ **Arsenic-associated OCM metabolites** affirmed and expanded our understanding of OCM in arsenic biotransformation.
- ❑ The metabolomic profiles of arsenic exposure and methylation capacity are both **more pronounced with inorganic than with methylated arsenicals**.
- ❑ Out of 20 top pathways in the FA-induced arsenic change analyses (D), **7 overlapped** with the baseline analyses. This suggests that these may be **arsenic-induced disruptions that could potentially be improved with FA supplementation**.
- ❑ While the novel findings require confirmation, they may enhance our understanding of **the mechanisms underlying arsenic-induced health outcomes** and may ultimately contribute to prevention and treatment strategies to **mitigate the adverse effects of arsenic exposure**.