Betaine, Choline and Carbon Metabolism: Beyond the Minimum Requirement

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Interest in dietary methionine (Met)

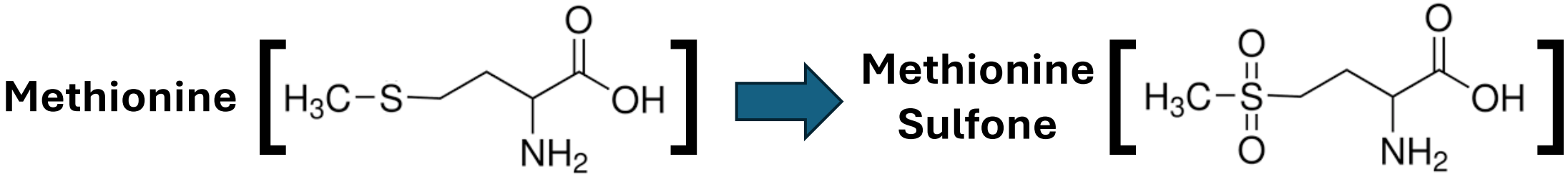
- **Met often first-limiting essential amino acid**

  (*Singh et al 2024*)

- **Met bioavailable may be unrecognizably low**
  - Ingredients & processing - variably oxidized Met content

    (*Smith et al 2021*)
  - Traditional dietary analytics measure oxidized Met as methionine sulfone

    (*Rutherfurd & Moughan 2008*)



Interest in dietary methionine

- **Met bioavailable may be unrecognizably low**
  - Dietary fiber effect (e.g., Stratton-Phelps et al 2002)
  - Antinutritional factors (e.g., Gupta 1987; Aletor 1993)
    - Digestive enzyme inhibitors, lectins, saponins, tannins, non-digestible oligosaccharides
    - Variably heat labile

Interest in dietary methionine

- **Met may be low secondary to low energy requirements**
  - **Met intakes per metabolic body weight, WIDELY VARY!**

	ME ***(kcal/day/kg$^{0.75}$)***	***Met*** ***(mg/day)***
Dogs (NRC RA)	95 – 200	110/*kg*$^{0.75}$
Cats (NRC RA)	55 – 260	42/*kg*$^{0.67}$

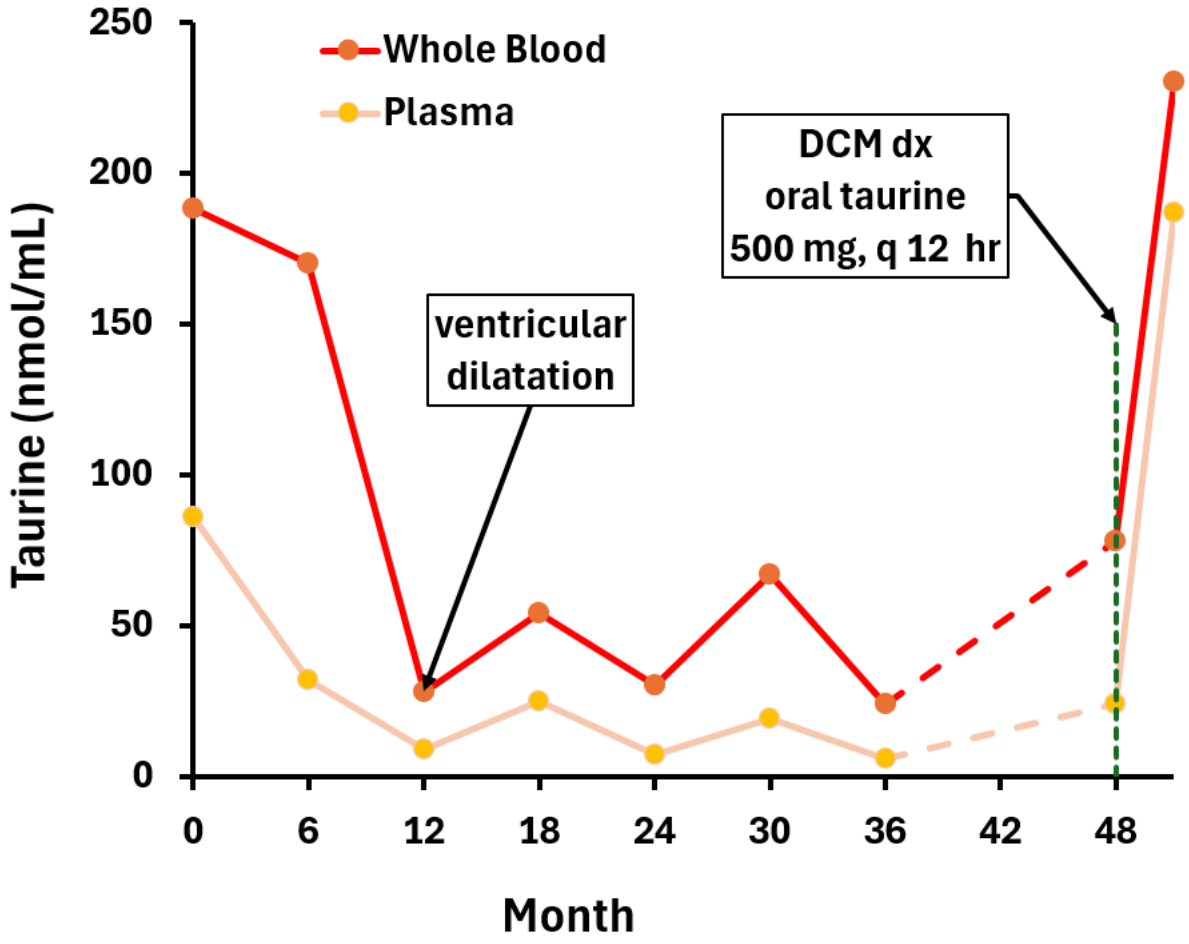
Met → → ~~→~~ taurine

Low dietary methionine associated with heart failure

… Reflected in low blood taurine

Sanderson et al 2001

- Beagles, n=18
  - Colony housed
  - 1-9 yr
- Diet
  - ~ 0.2% met DMB (0.33% NRC RA)
  - 10% protein
  - No taurine supplementation
- 1 of 17 dx DCM @ 48 months
- Taurine tx, “reversed” DCM



Consequences of methionine inadequacy

Dogs: Diet-associated taurine-deficiency Dilated cardiomyopathy (DCM)?

Received: 8 December 2023 | Accepted: 16 July 2024

DOI: 10.1111/jvim.17150

STANDARD ARTICLE

Journal of Veterinary Internal Medicine Open Access

ACVIM American College of Veterinary Internal Medicine

The association between taurine concentrations and dog characteristics, clinical variables, and diet in English cocker spaniels: The Canine taURinE (CURE) project

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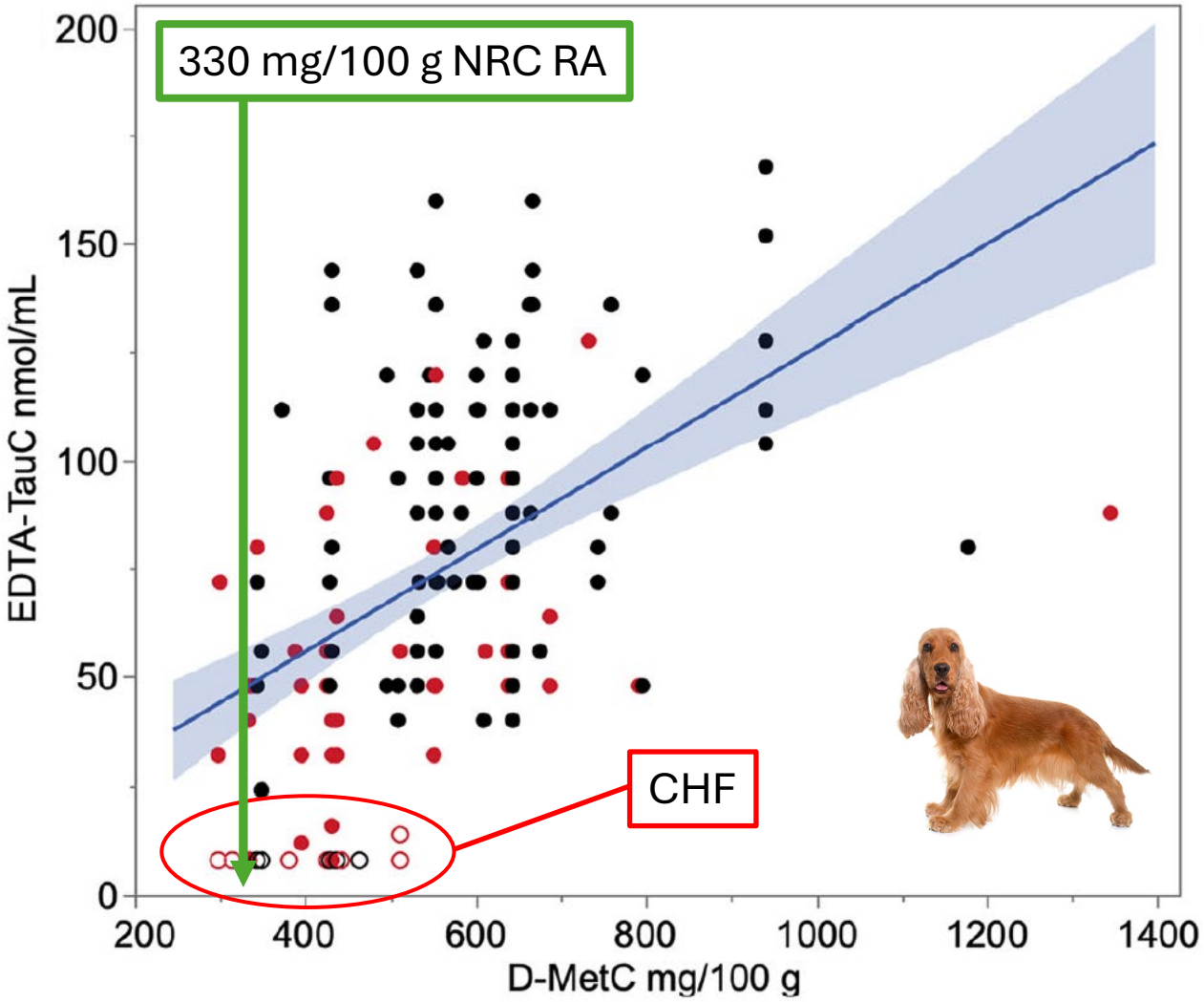
- **English Spaniels, n=183**
  - Privately owned
  - 1.7 to 6.3 y
  - 13 of 180 dx CHF
- **Diets**
  - ~ 0.2 to 1.3% met DM
- **Diet met vs plas, Tau**
  - Correlated ($p < 0.001$)
  - CHF, low met & taurine



Kriström et al 2024 Taurine concentrations and dog characteristics, clinical variables, and diet in English cocker spaniels

Diet-associated DCM

Not always associated with taurine deficiency

- **Dogs** (Freeman et al 2018)

Commentary

Diet-associated dilated cardiomyopathy in dogs: what do we know?

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Joshua A. Stern DVM, PhD
Ryan Fries DVM
Darcy B. Adin DVM
John E. Rush DVM, MS

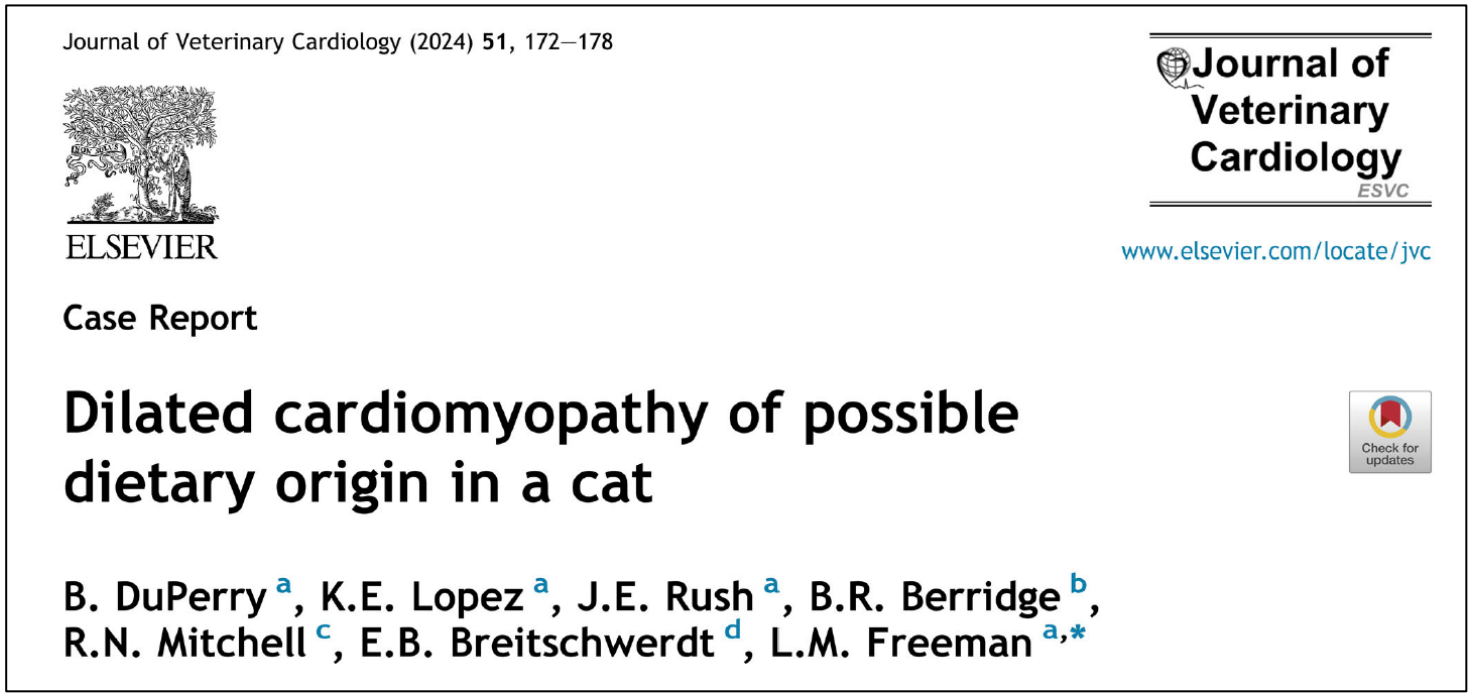
From the Department of Clinical Sciences, Cummings School of Veterinary Medicine, Tufts University, North Grafton, MA 01536 (Freeman, Rush); Department of Medicine and Epidemiology, School of Veterinary Medicine, University of California-Davis, Davis, CA 95616 (Stern); Department of Veterinary Clinical Medicine, College of Veterinary Medicine, University of Illinois, Urbana, IL 61802 (Fries); and Department of Clinical Sciences, College of Veterinary Medicine, North Carolina State University, Raleigh, NC 27607 (Adin).

Address correspondence to Dr. Freeman (lisa.freeman@tufts.edu).

Diet-associated DCM

Not always associated with taurine deficiency

- **Dogs** (Freeman et al 2018)
- **Cats** (DuPerry et al 2024)



Journal of Veterinary Cardiology (2024) **51**, 172–178

ELSEVIER

Journal of Veterinary Cardiology ESVC

www.elsevier.com/locate/jvc

Case Report

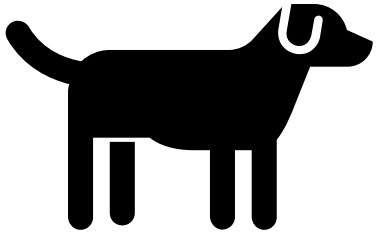
Dilated cardiomyopathy of possible dietary origin in a cat

B. DuPerry [a], K.E. Lopez [a], J.E. Rush [a], B.R. Berridge [b], R.N. Mitchell [c], E.B. Breitschwerdt [d], L.M. Freeman [a,*]

Methionine-deficiency DCM?

Methods to assess methionine status in adults

- Blood taurine concentration
  - Useful for dogs
    1. *Sanderson et al 2001*
    2. *Tôrres et al 2022*
    3. *Kriström et al 2024*



  - BUT, now confounded by dietary taurine supplementation

Report	***n***	***mg/kg DM***
Leavitt et al 2025	20	2,800 (1,600 – 4,600)
Freeman et al 2001	28	295 (100 – 1,300)
AAFCO Cat Diets	-	1,000 (dry), 2,000 (canned)

Methionine-deficiency DCM?

Methods to assess methionine status

- Plasma methionine concentration
  - Not useful for dogs, for cats?
  - Homeostatically regulated in rats (Finkelstein & Martin 1986)
  - Appears homeostatically regulated in dogs of large size (> 20 kg)
    1. Harrison et al 2020
    2. Mansilla et al 2020
    3. Leavitt et al 2025

Methionine-deficiency DCM?

Methods to assess methionine status

- Plasma betaine concentration
  - Apparently useful for large dogs
  - Harrison et al 2020 (Labrador Retrievers)

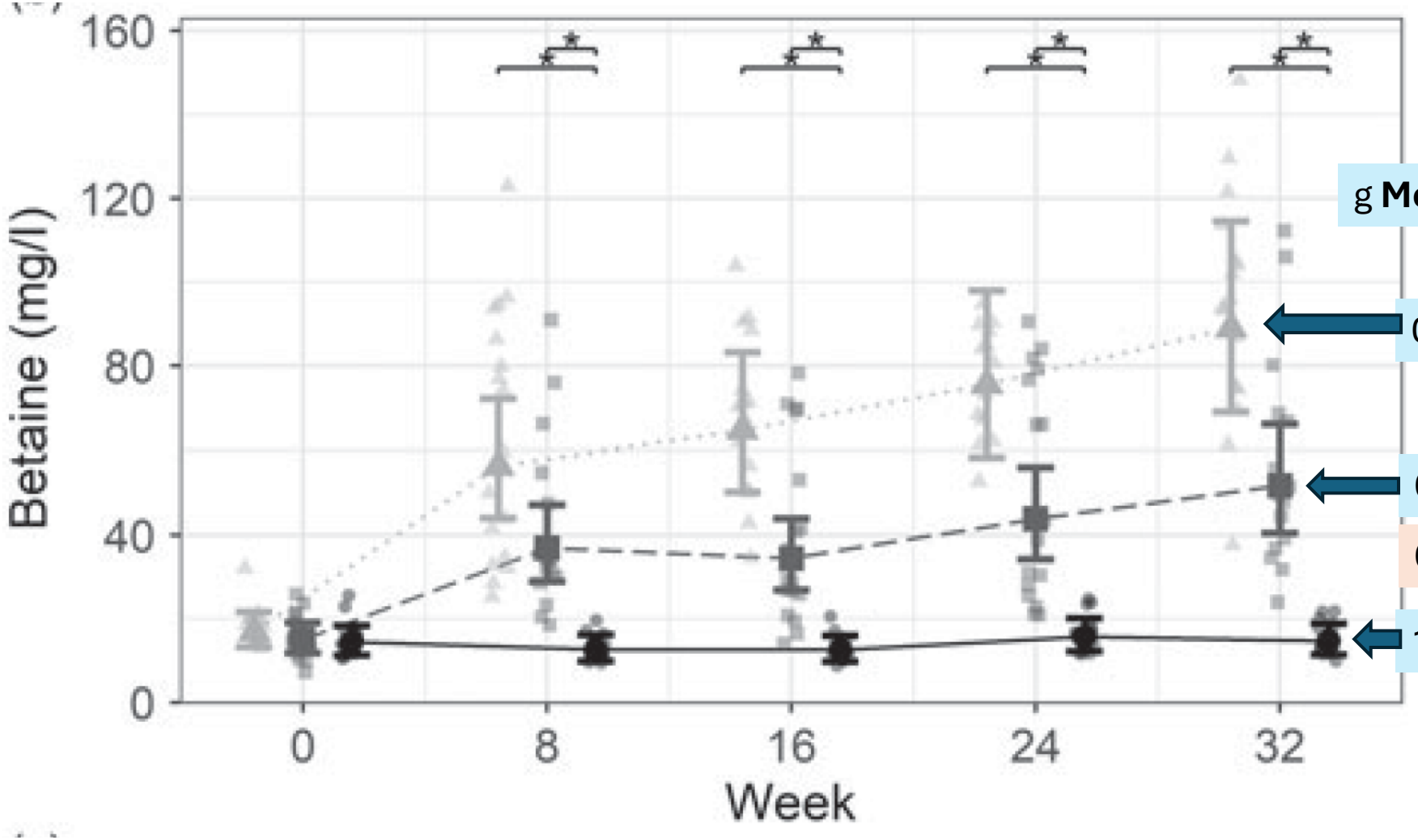
British Journal of Nutrition (2020), 123, 1333–1344
doi:10.1017/S0007114520000690

Short-term determination and long-term evaluation of the dietary methionine requirement in adult dogs

Matthew Harrison*, Gaelle Thomas, Matthew Gilham, Kerry Gray, Alison Colyer and David Allaway
WALTHAM Centre for Pet Nutrition, Freeby Lane, Waltham-on-the-Wolds, Leicestershire LE14 4RT, UK

Plasma betaine as an indicator of dietary Met concentration

Harrison et al 2020 … dietary protein, ~25% DM, taurine; ~ 1.0 g/kg DM

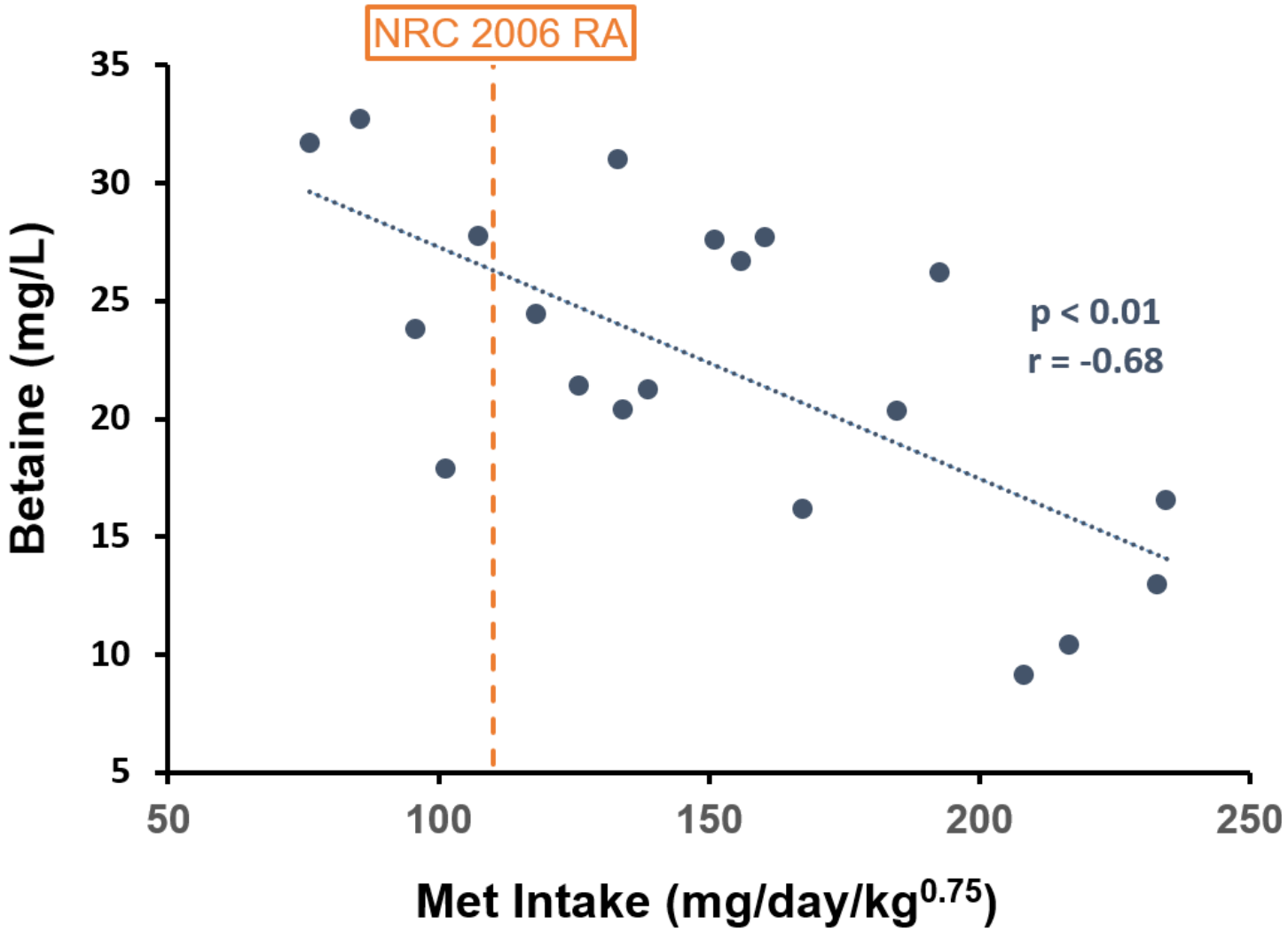


g **Met**/Mcal	(% DM)	
0.55	(0.20)	
0.71	(0.26)	
0.83	(0.33)	NRC RA
1.37	(0.56)	

Plasma betaine as an indicator of dietary Met intake

Leavitt et al 2025, 20 large (21 to 34 kg) dogs, varies commercial diets

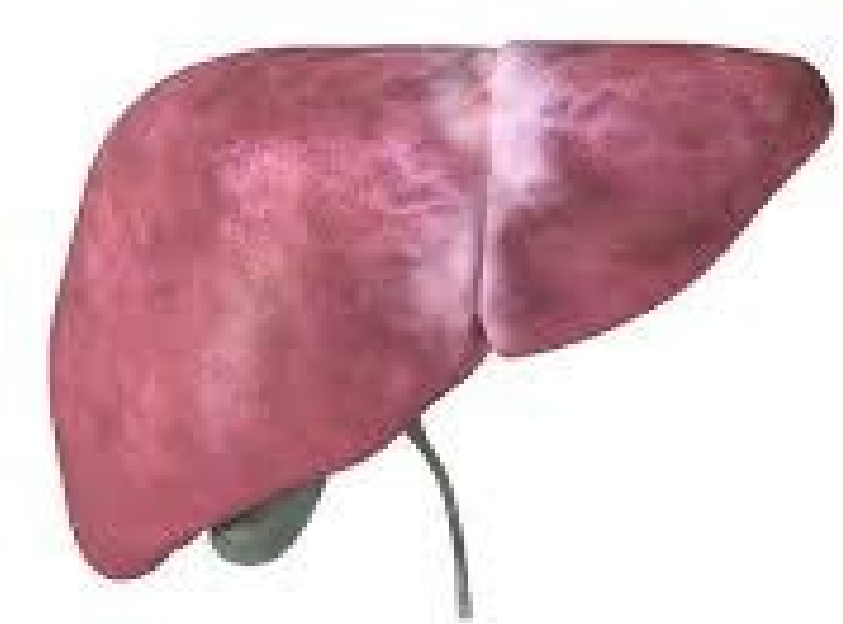
- **Plasma betaine**
  - ~ 250% variation
- **Met intake**
  - ~ 200% variation
  - Inversely correlated
  - 5 of 20 dogs < NRC RA



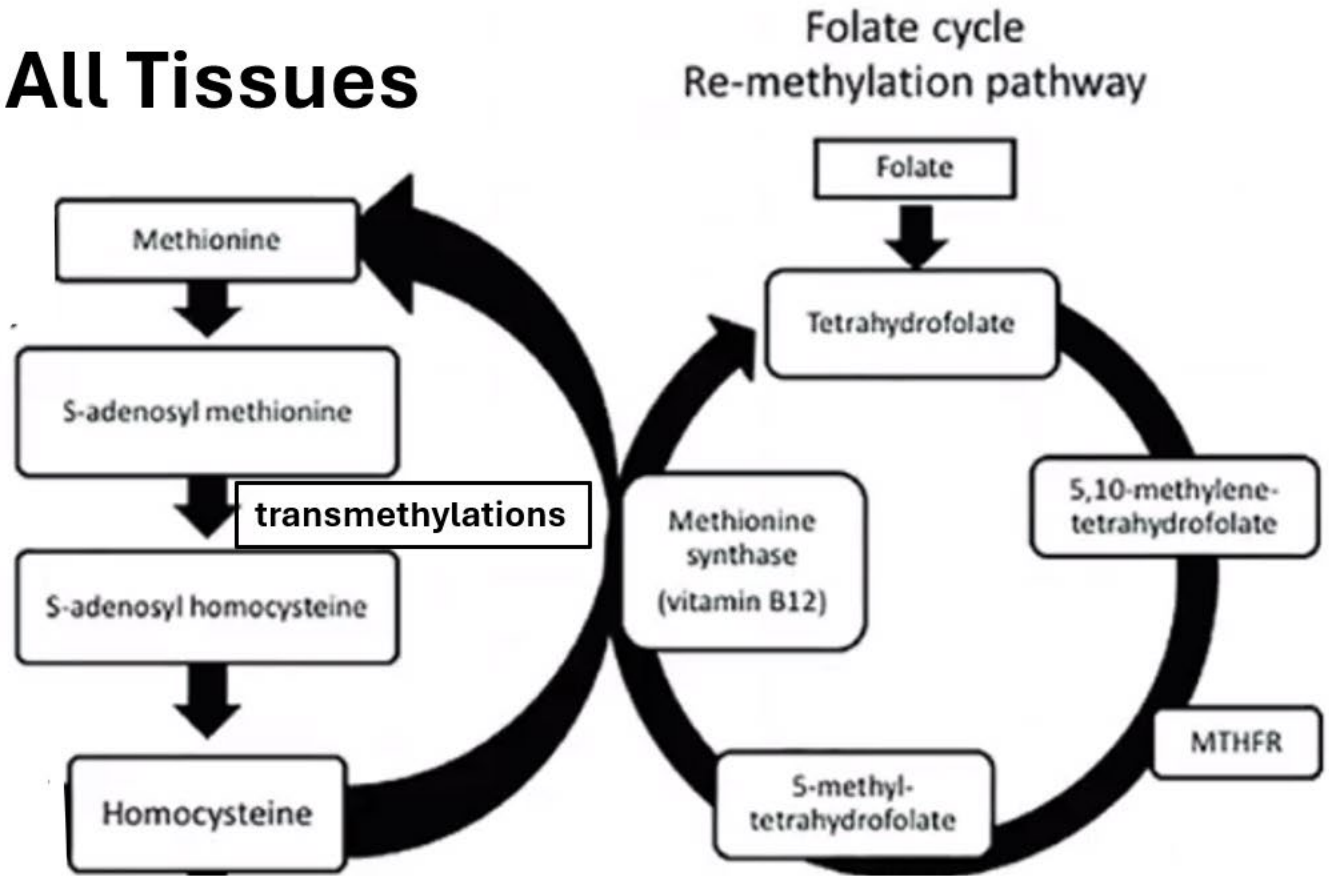
✓ **High plasma betaine may signal Met inadequacy**

BUT, Why?

…. when ↓ Met intake, ↑ plasma betaine



All Tissues


Folate cycle
Re-methylation pathway
Folate
Tetrahydrofolate
5,10-methylene-
tetrahydrofolate
MTHFR
5-methyl-
tetrahydrofolate
Methionine
synthase
(vitamin B12)
Methionine
S-adenosyl methionine
transmethylations
S-adenosyl homocysteine
Homocysteine

Liver

Re-methylation pathway

DMG

BHMT

Betaine

Choline

Methionine

S-adenosyl methionine

transmethylations

S-adenosyl homocysteine

Homocysteine

CBS (vitamin B6)

Cystathionine

Cysteine

glutathione

taurine

Transsulfuration pathway

Folate cycle
Re-methylation pathway

Folate

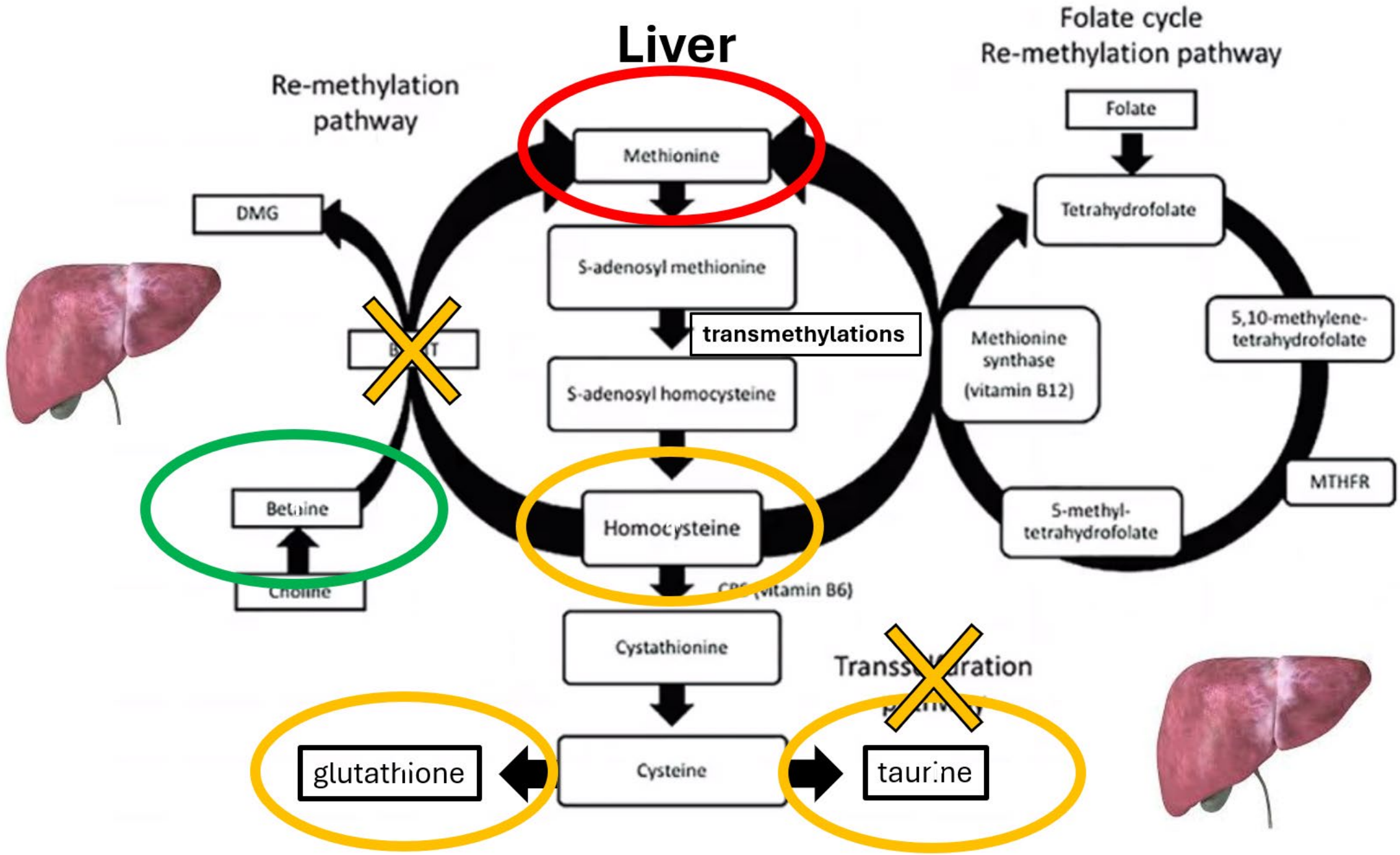
Tetrahydrofolate

5,10-methylene-tetrahydrofolate

MTHFR

5-methyl-tetrahydrofolate

Methionine synthase (vitamin B12)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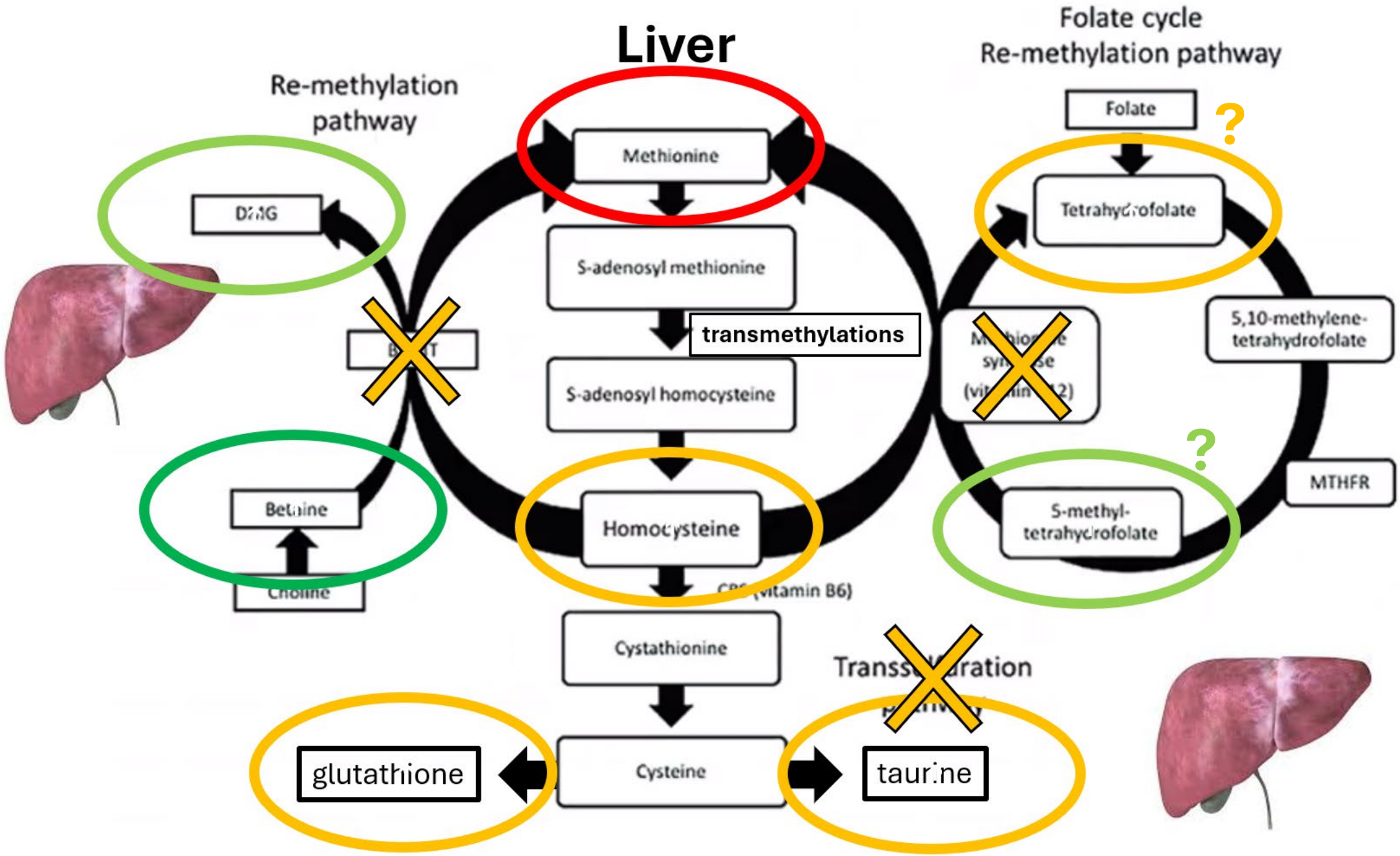
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5,10-methylene-tetrahydrofolate
MTHFR
5-methyl-tetrahydrofolate
Betaine
Choline
(vitamin B6)
?
?

High plasma betaine …

Might or might not indicate body protein synthesis reduction

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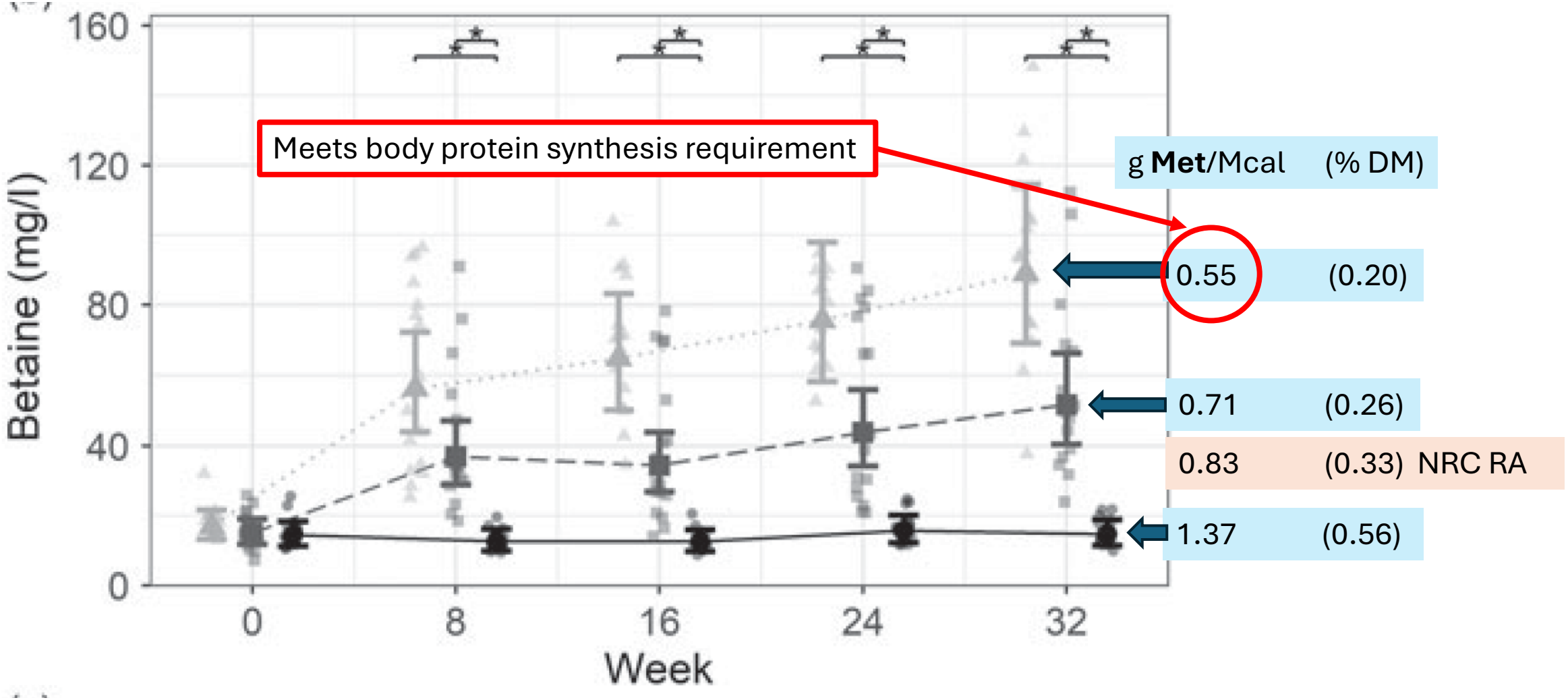


High plasma betaine …

Could indicate coincident Met limiting …

- **Liver glutathione (GSH) & taurine production**

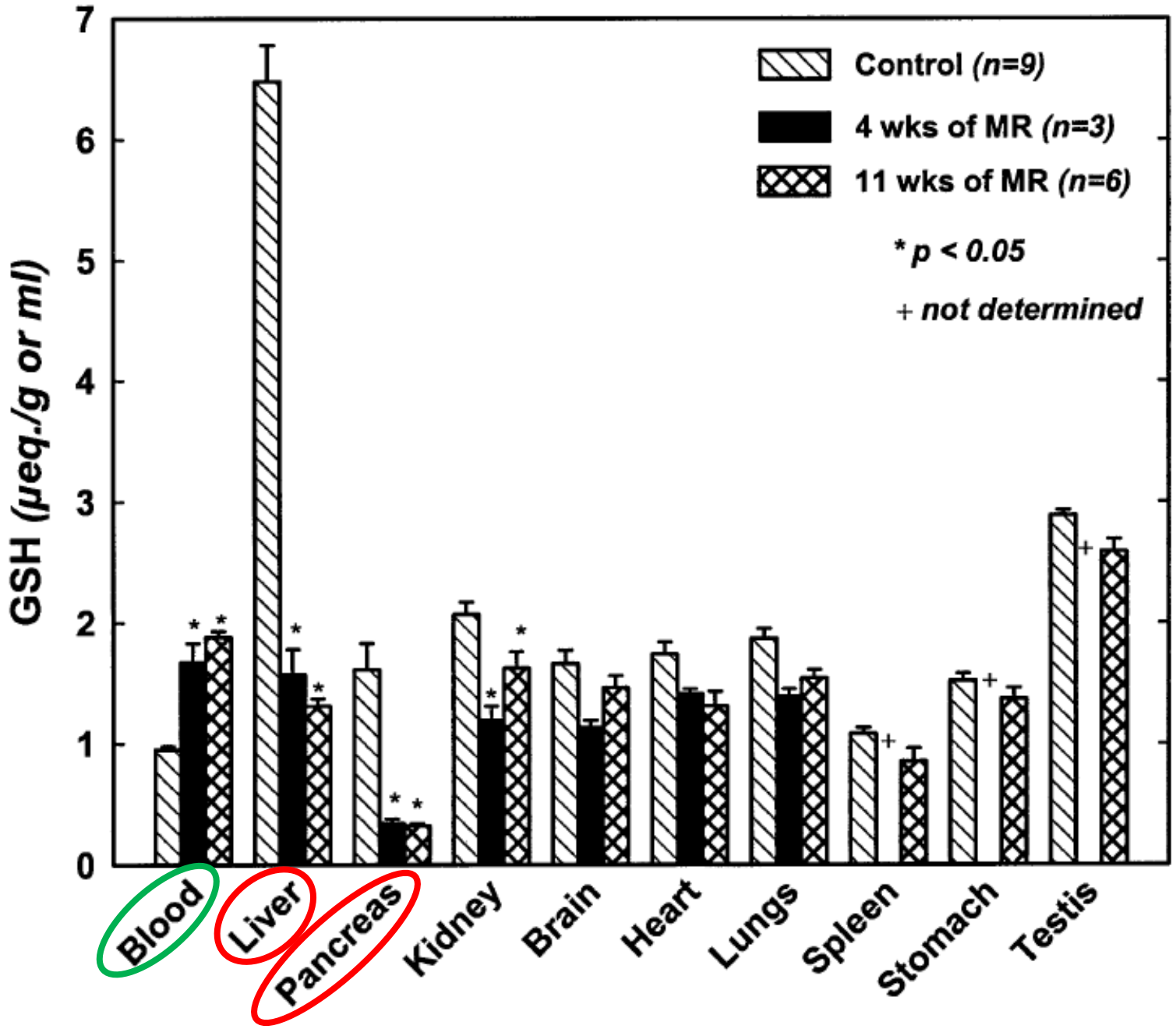
  MET → HOMOCYSTEINE → CYSEINE → GSH & taurine

- **Diet Met restriction of rats** (*Richie et al 2004*)

  ↓ GSH in liver & pancreas

Glutathione (GSH)

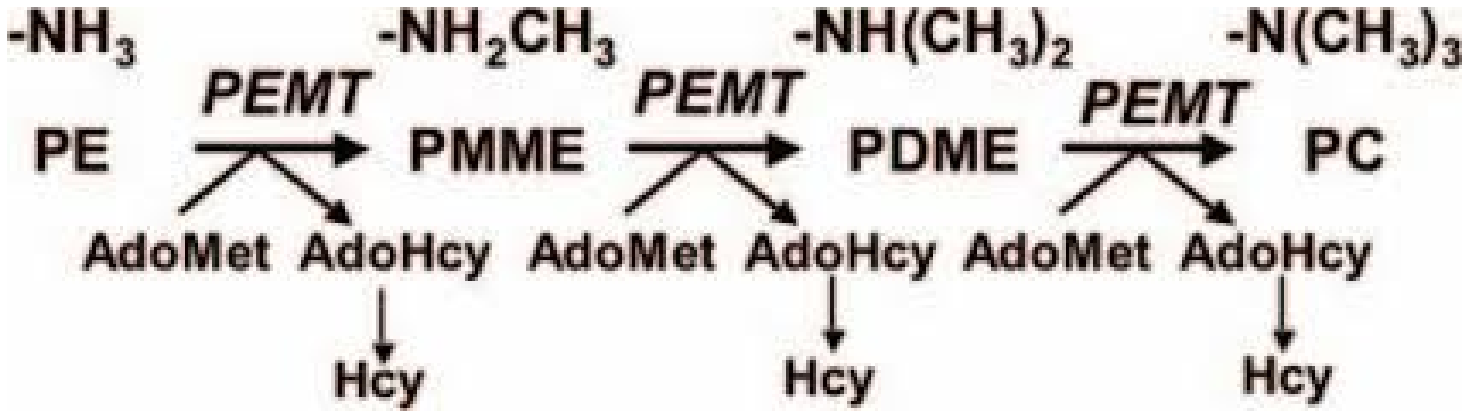
Richie et al 2004 Tissue glutathione and cysteine levels in methionine-restricted rats



High plasma betaine …

Might indicate coincident methionine limiting for liver transmethylations need for …

- **Creatine**
- **Phosphatidylcholine**



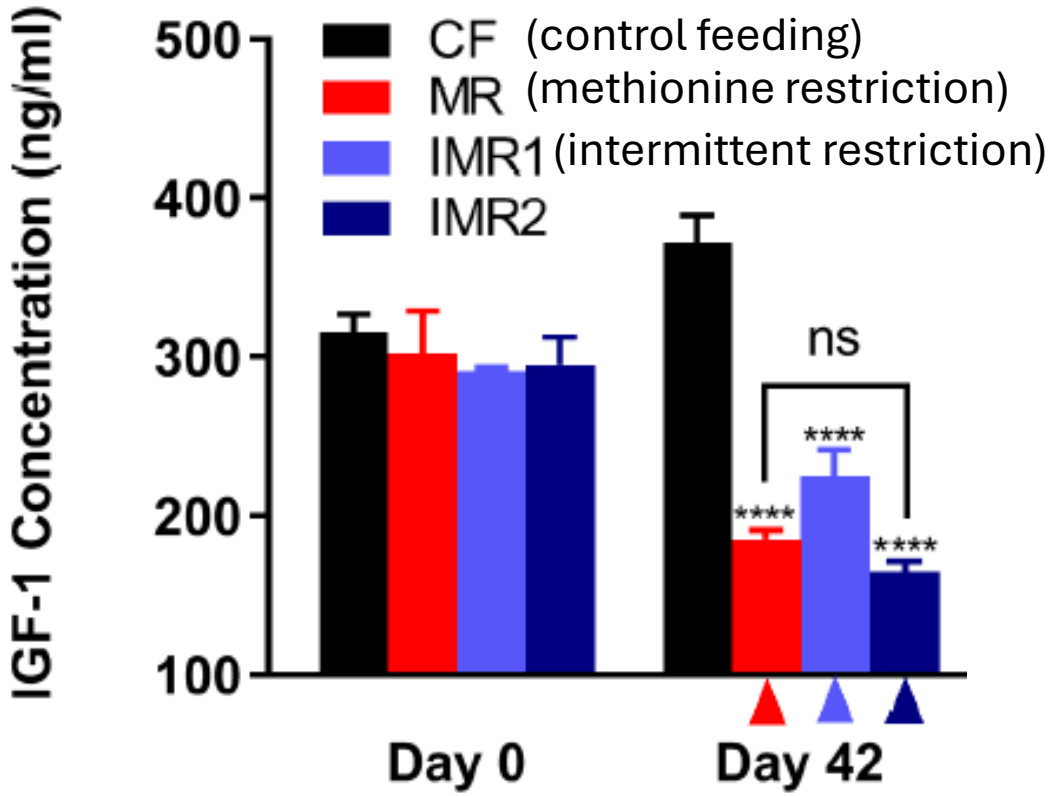
- **Cellular chromatin structure, gene expression**

High plasma betaine …

Might indicate coincident hormonal changes induced by Met restriction as in rodents and humans

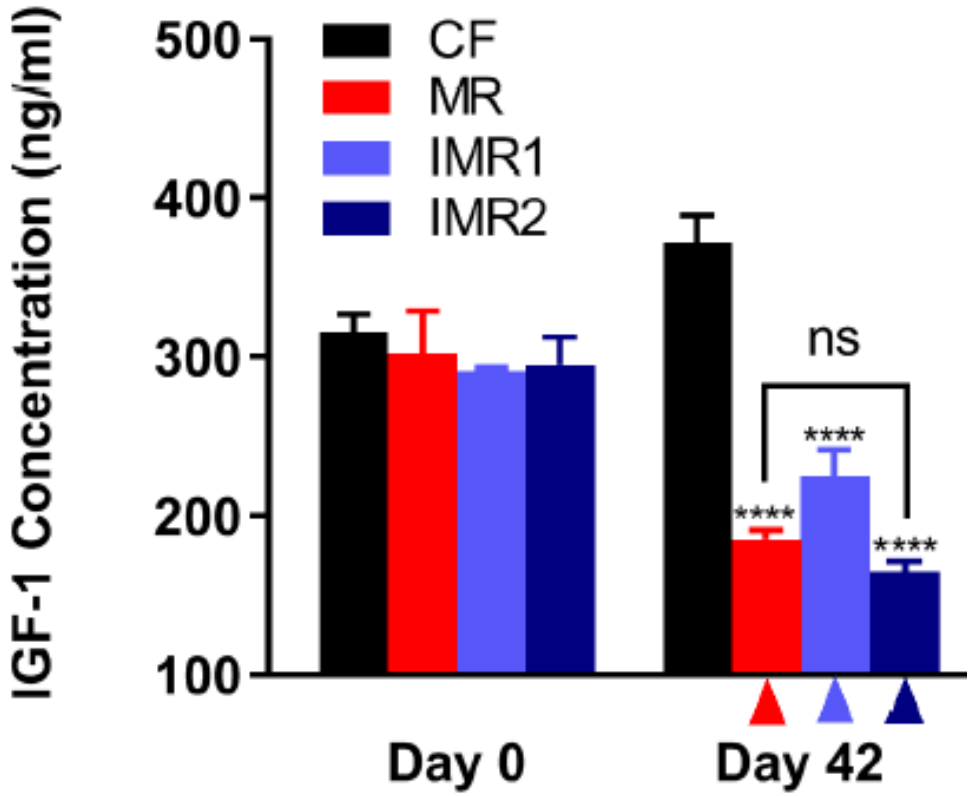
- **Hormones**
  - **↓ Insulin-like growth factor (IGF-1)**
  - **↑ Fibroblastic growth factor (FGF-21)**

Plasma IGF-1

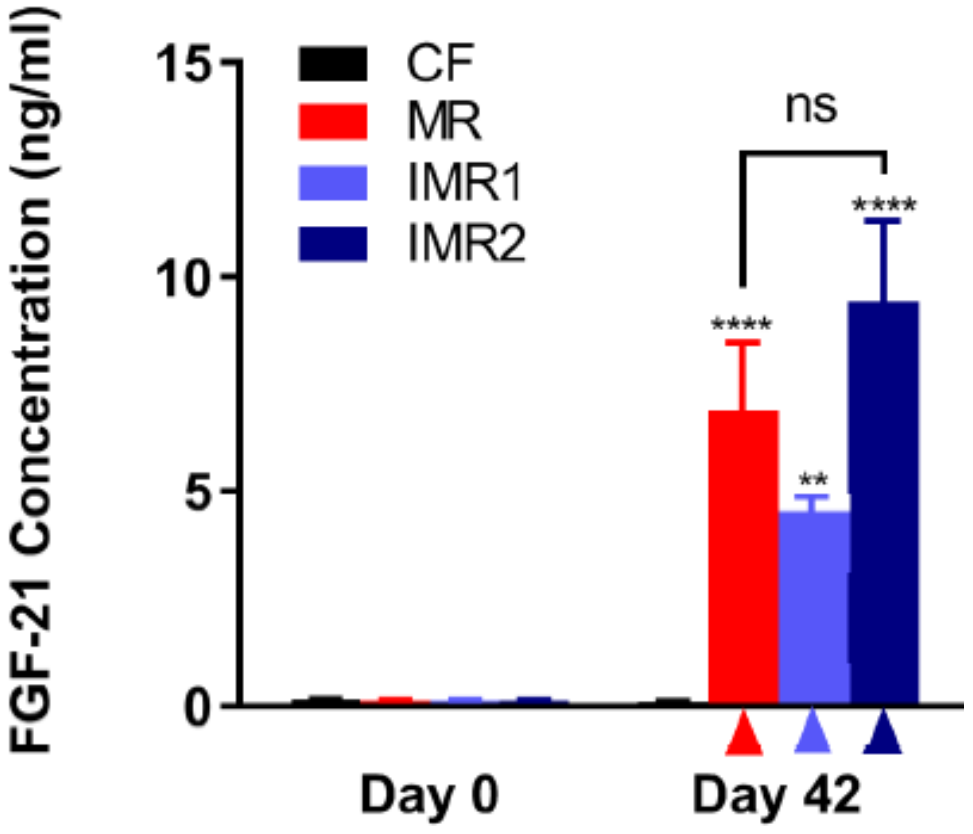


Plummer & Johnson 2022 Intermittent methionine restriction reduces IGF-1 levels and produces similar healthspan benefits to continuous methionine restriction

Plasma IGF-1



Plasma IGF-21



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Knowledge Gaps for future study

Met restriction or inadequacy

- Betaine elevation in small dogs? In cats?
- Causative of or contributing to DCM in dogs and cats?
  - Declining IGF-1, rising FGF-23
  - Deficit in transmethylation activities
    1. Plasma ↓ creatine: betaine ratio
    2. Plasma ↓ creatine: guanidinoacetic acid ratio
    3. Plasma ↓ phosphatidylcholine:phosphatidylethanolamine ratio
- Depleting of GSH in liver in dogs and cats?