Metabolomic Insights into Kidney Disease Progression

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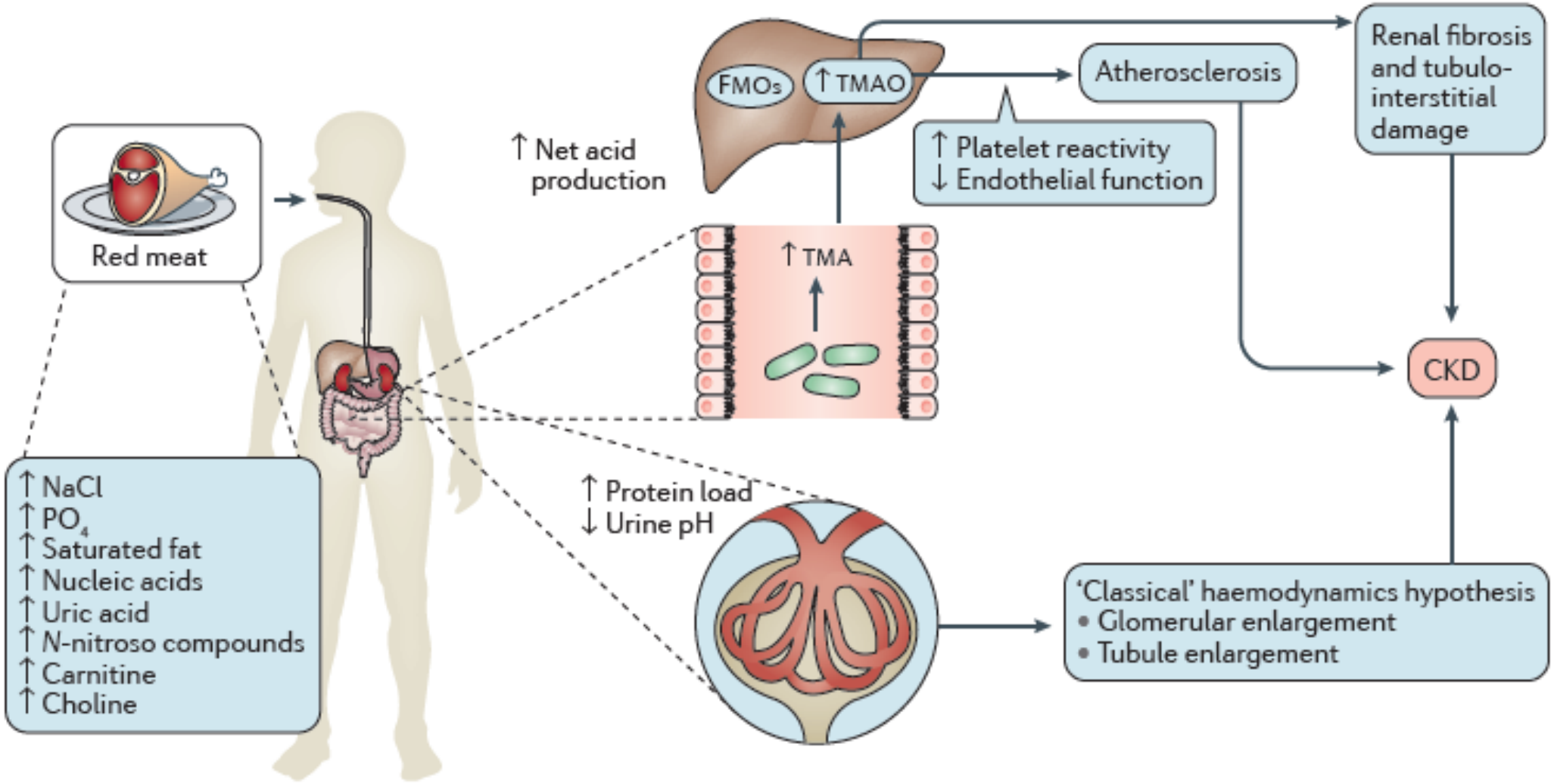
Disclaimers

- Participate in advisory board with Gilead Sciences, Baxter Healthcare
- Participate in research with Travere Therapeutics, Alpine Immune Sciences, Vera Therapeutics, Novartis, AstraZeneca, Boehringer Ingelheim, Bayer, Otsuka
- Speaker for AstraZeneca, Boehringer Ingelheim, Otsuka Pharmaceutical, Baxter, Fresenius Medical Care
- Research grant from AstraZeneca, Boehringer Ingelheim

Early observation: effect of red meat intake on kidney function

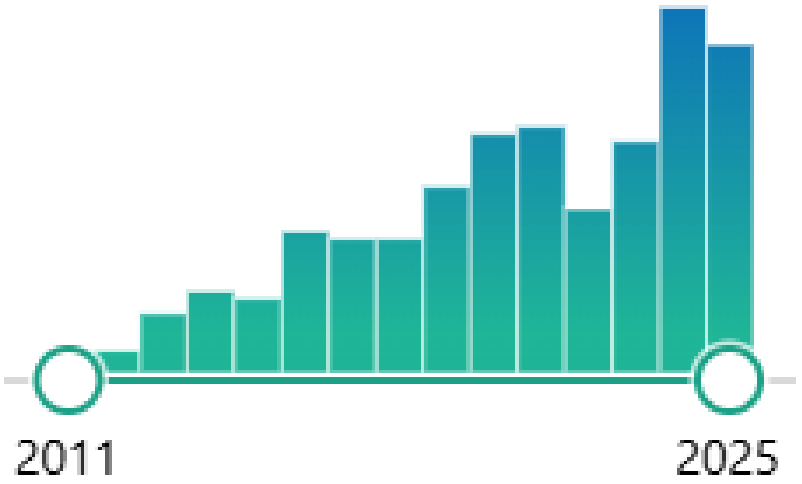


Peter Stenvinkel. Nat Rev Nephrol 2018; 265.

*FMO: Flavin-containing monooxygenase (enzyme for the generation of TMAO)

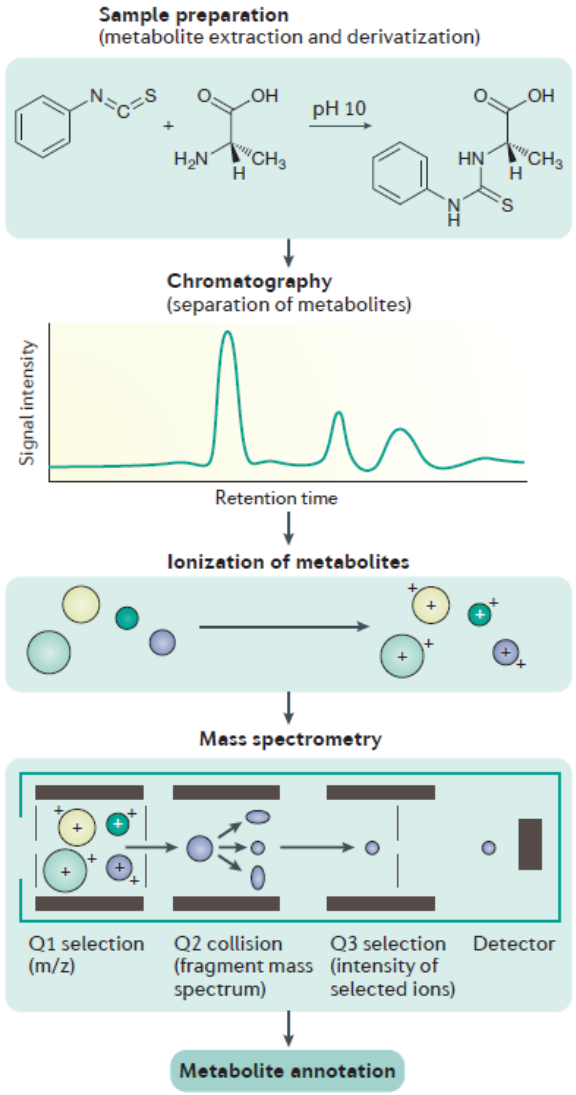
Metabolomic study and CKD: some questions

no. of publications in PubMed on
“chronic kidney disease” and “metabolomic”

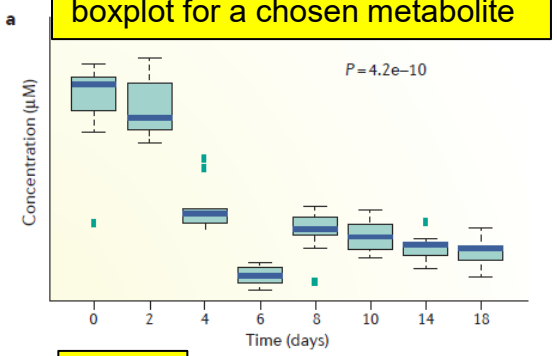


- How ? method of study
- Which ? metabolite species of interest
- What ? clinical implications
- Why ? mechanism of the effect

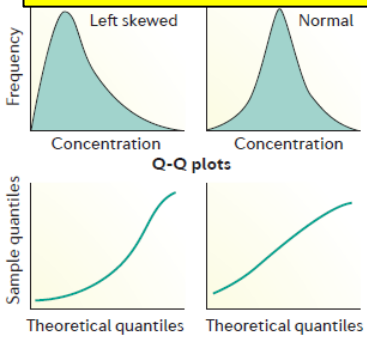
Metabolomics: methods in a nutshell



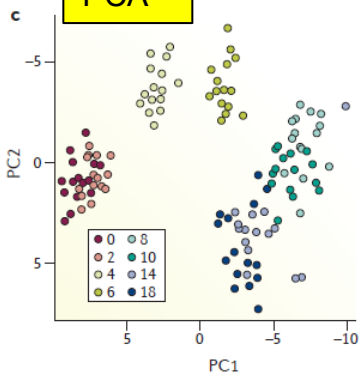
boxplot for a chosen metabolite



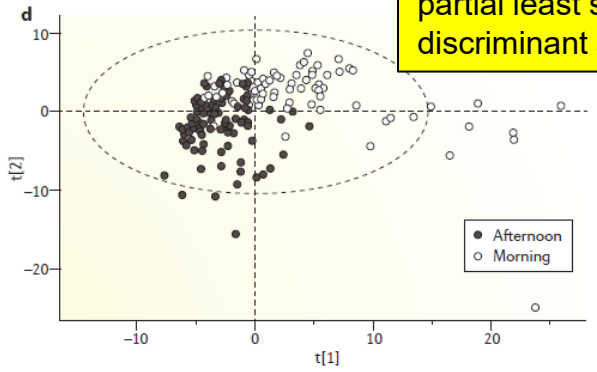
data distribution: histogram and QQ plots



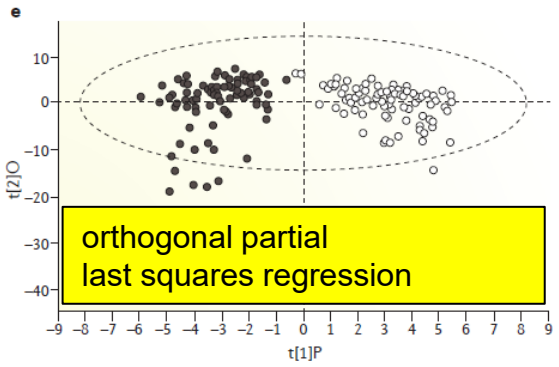
PCA



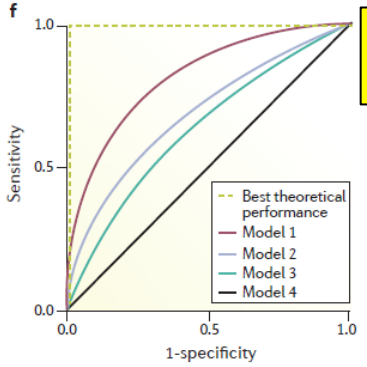
partial least squares regression discriminant analysis (PLS-DA)



orthogonal partial last squares regression



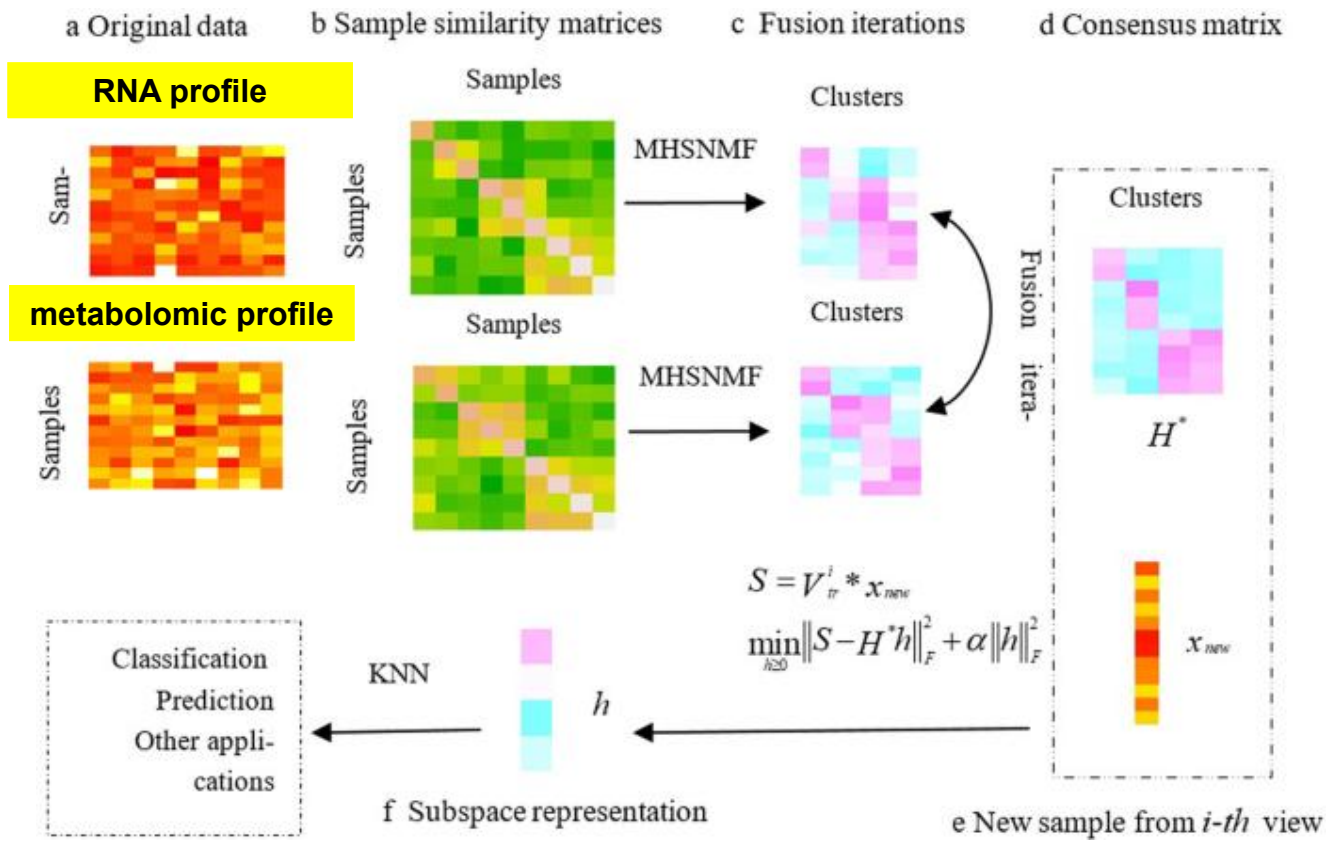
ROC curve



Hocher B.
Nat Rev Nephrol.
2017 May;13(5):269-284.

From metabolomic to multi-omic study

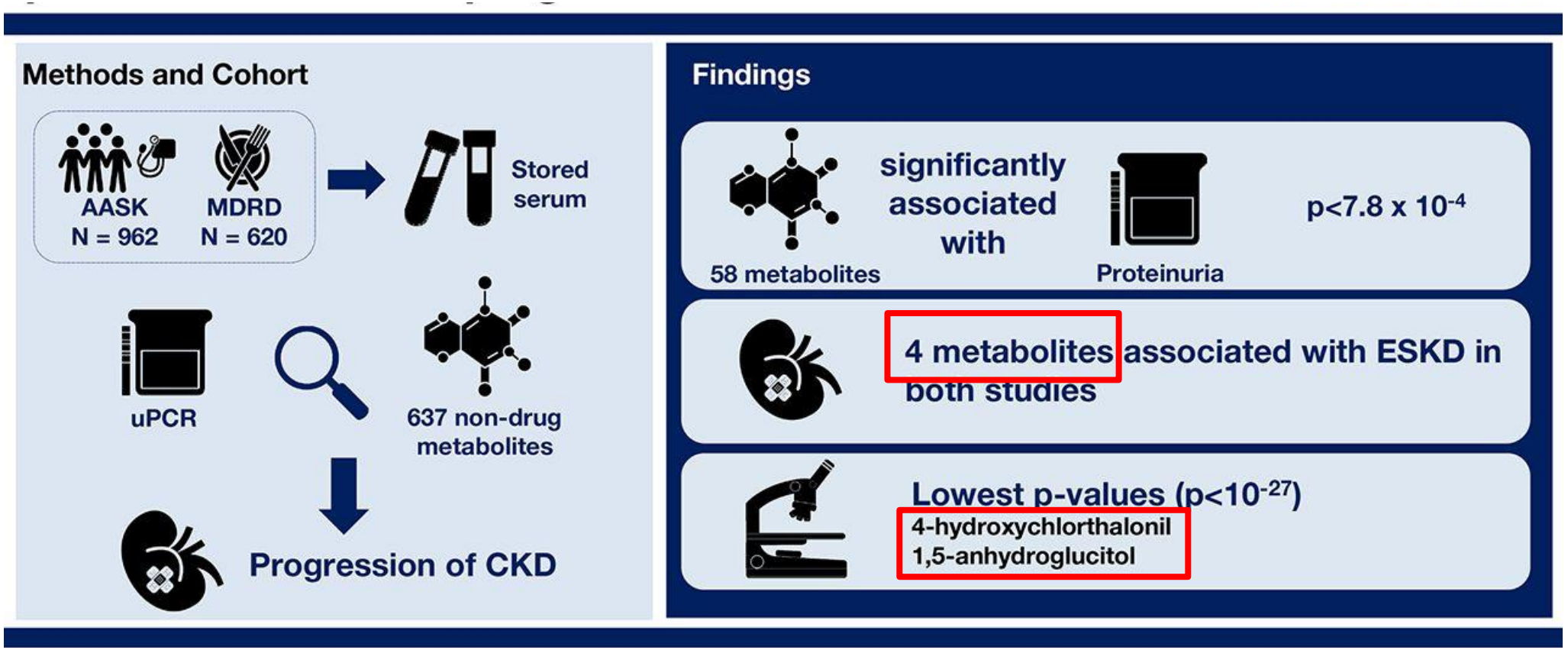
non-negative matrix factorization (NMF) clusters for molecular subgroups



*MHSNMF: multi-view hessian regularization based symmetric nonnegative matrix factorization

Bhatt BJ. Nature 2025; 646: 973
Ma Y. BMC Bioinformatics 2020; 21: 234

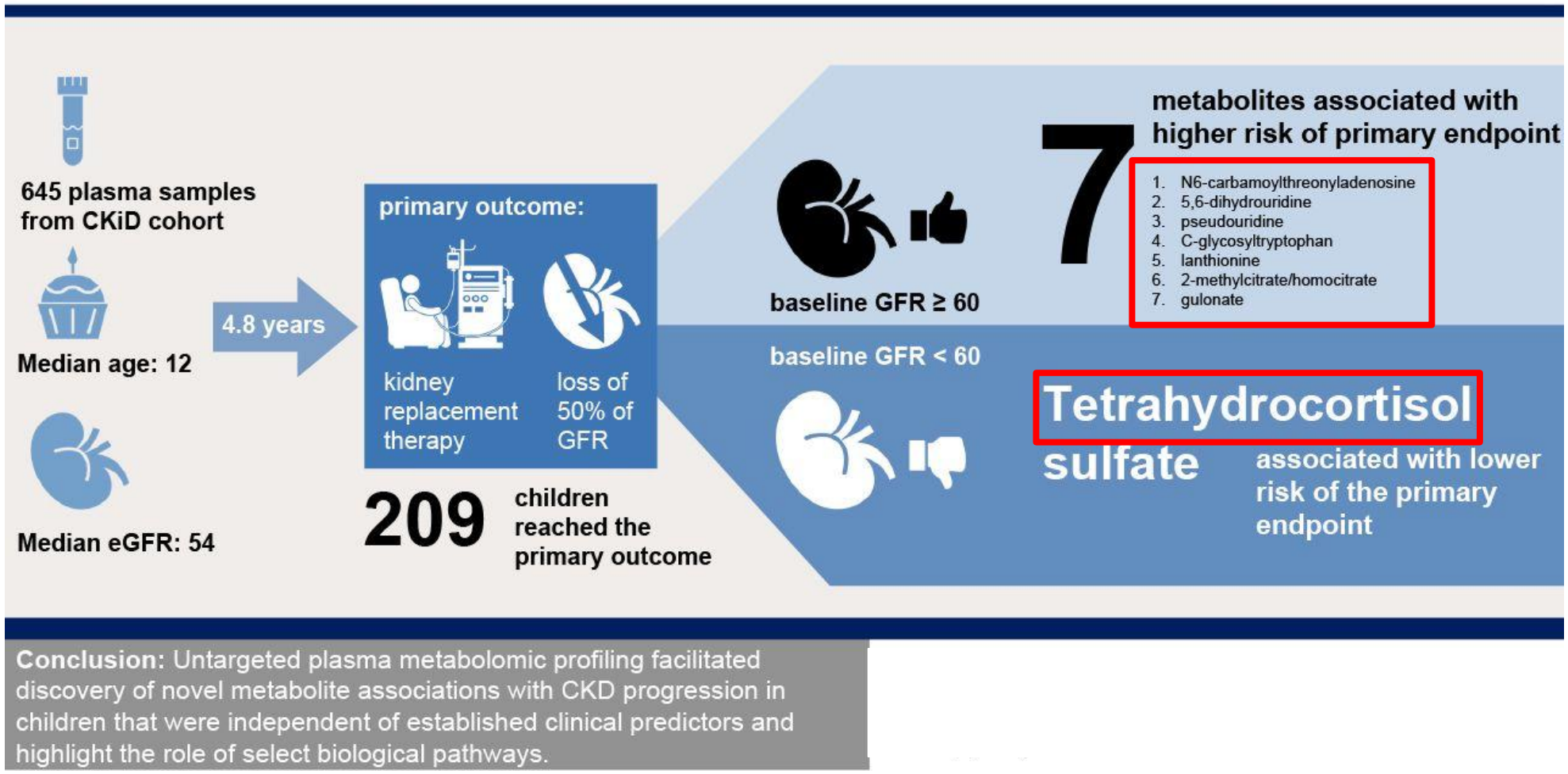
Serum metabolomic alterations a/w proteinuria in CKD



Conclusions We identified 58 serum metabolites with cross-sectional associations with proteinuria, some of which were also associated with CKD progression.

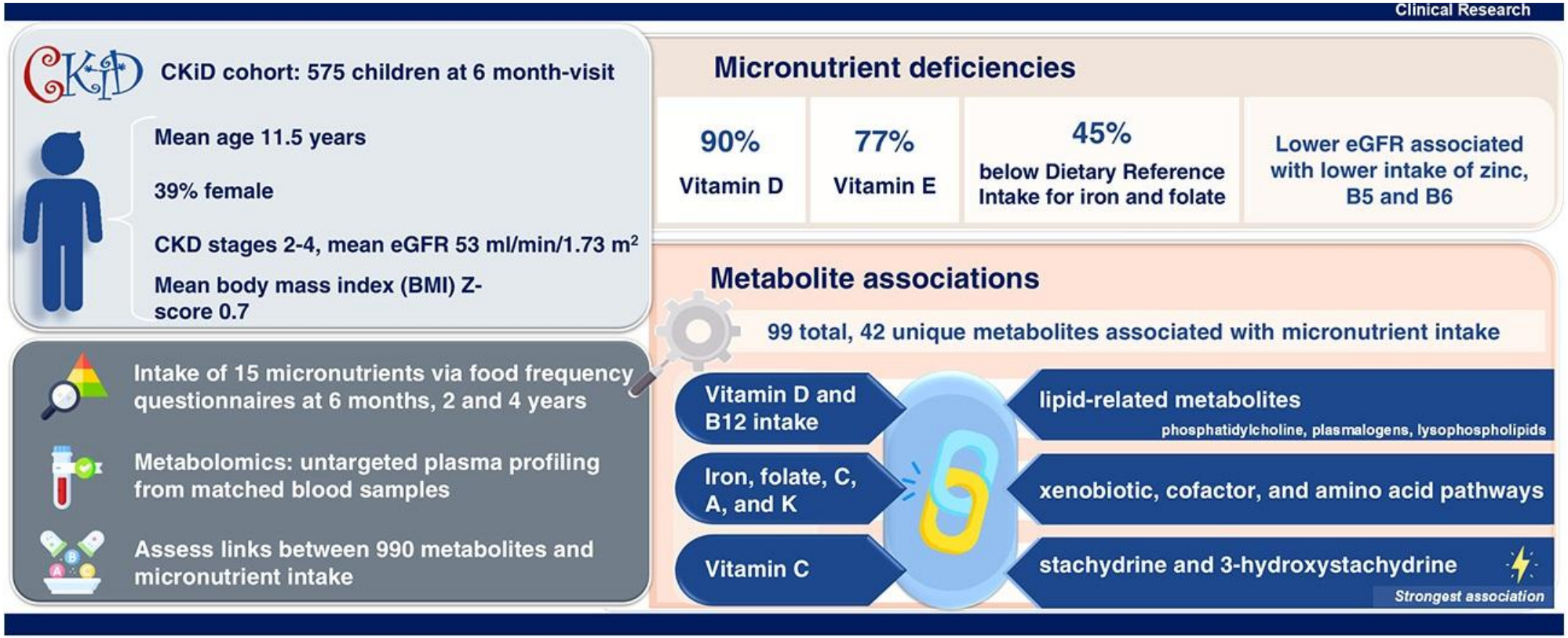
Shengyuan Luo. CJASN March 2019, 14 (3) 342-353

Metabolite biomarkers of CKD progression in children



Denburg MR.
Clin J Am Soc Nephrol. 2021 Aug;16(8):1178-1189.

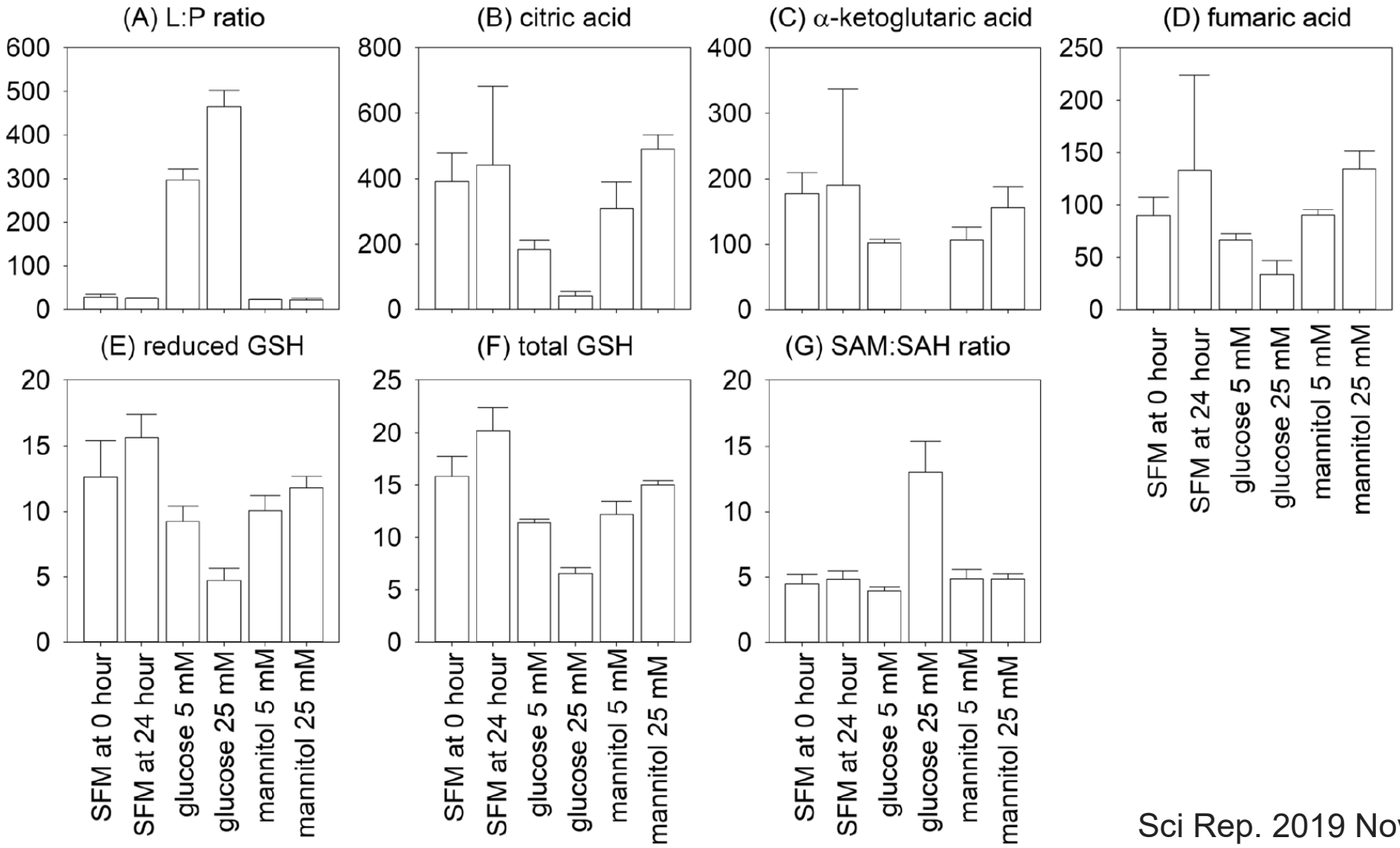
Dietary Micronutrient Intake and Metabolome in CKD



Conclusions: The majority of children with CKD have intake below dietary reference intake of at least one micronutrient despite normal BMI, which was associated with alterations in lipid metabolism.

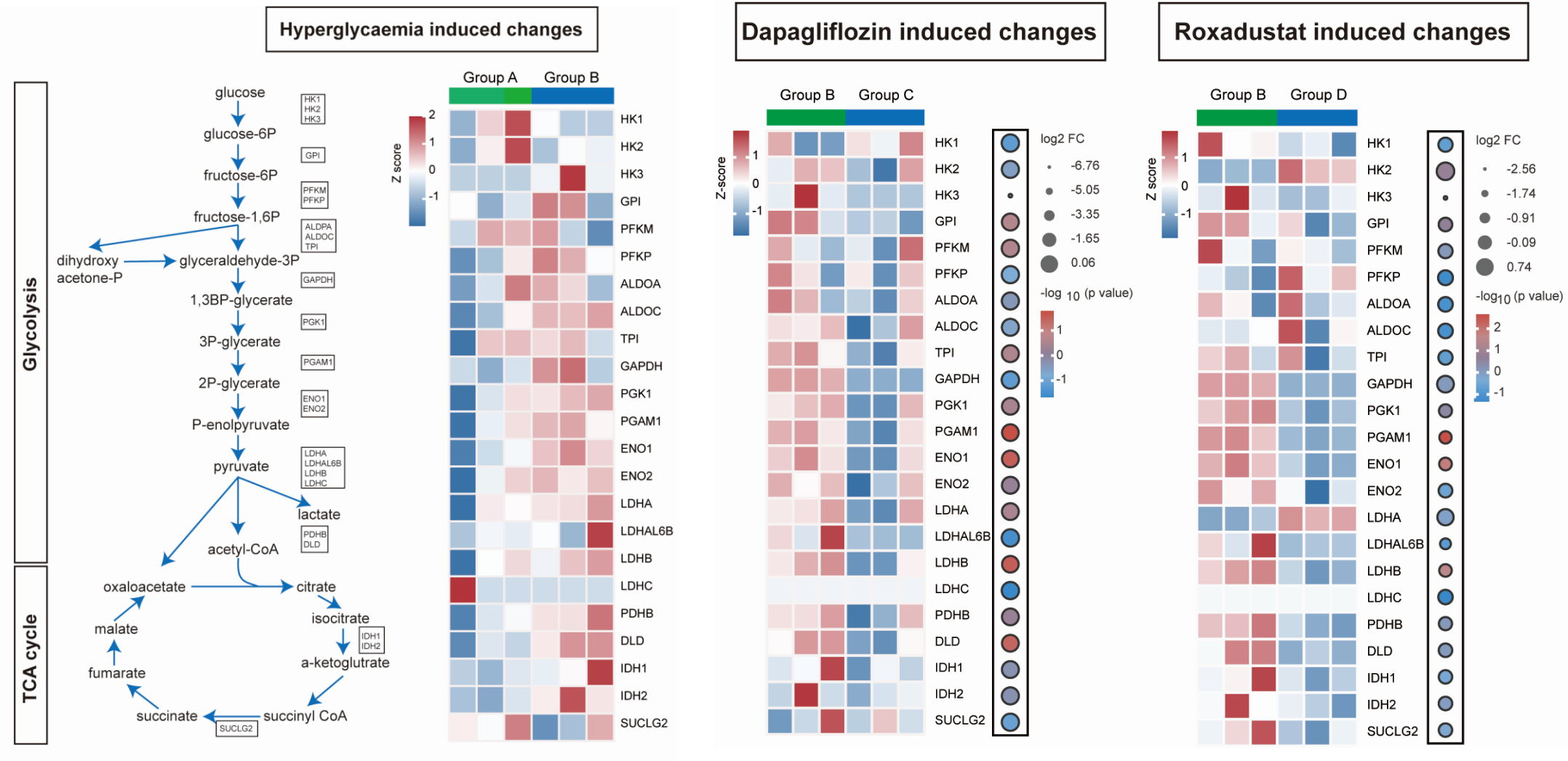
Denise C. Hasson.
Clin J Am Soc Nephrol 2025; 20:1536

Cell specific metabolomic change: PTC in high glucose



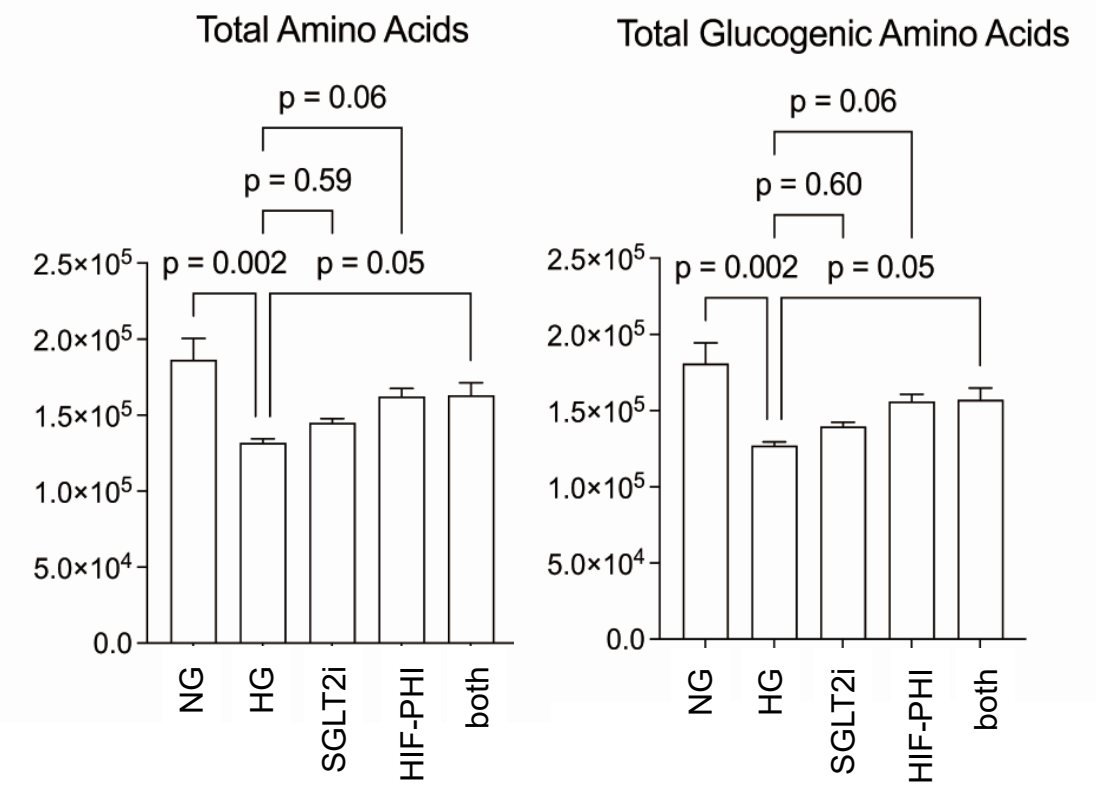
Wei PZ.
Sci Rep. 2019 Nov 12;9(1):16617.

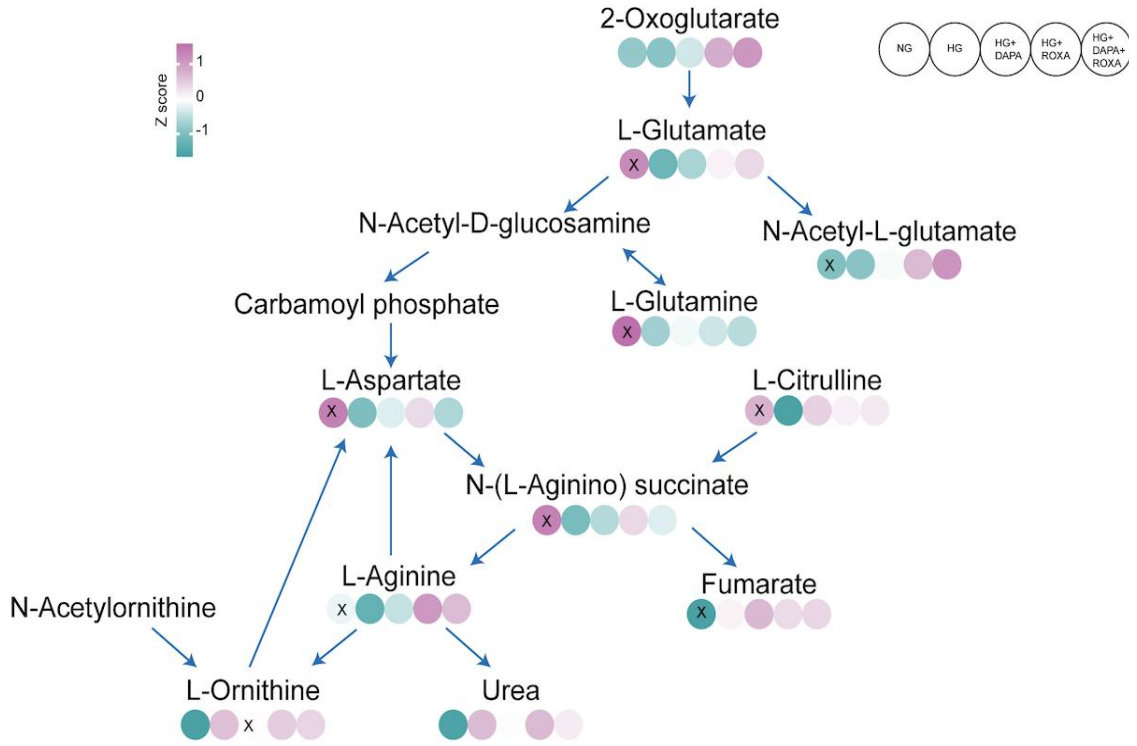
cf. metabolomic change of podocyte



Li CL. manuscript under review

Change in amino acid profile and arginine / NO pathway





*HIF hydroxylation require alpha ketoglutarate as co-substrate

Li CL. manuscript under review

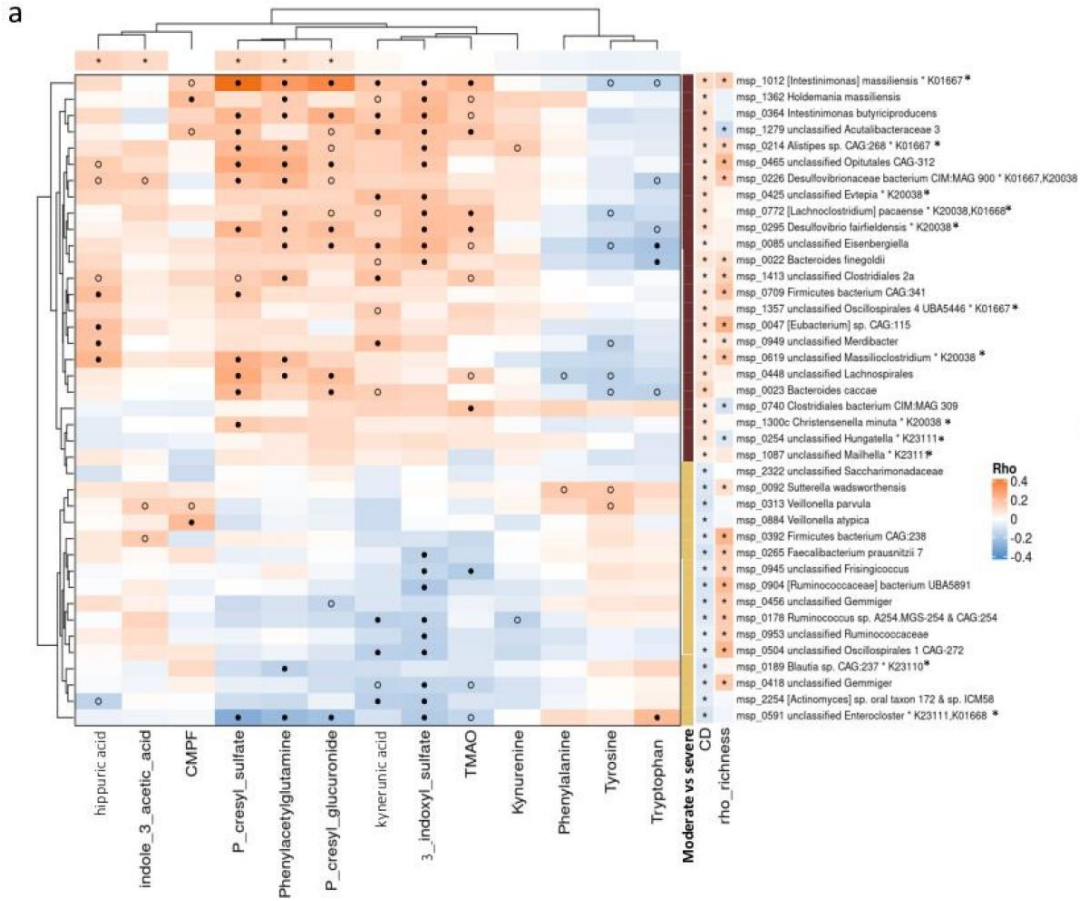
Metabolome: not only our own metabolites

- MASLD and CKD are linked through mechanisms like lipid accumulation and oxidative stress
- gut dysbiosis leads to harmful metabolites that affect kidney function
  - toxins from the gut can cause systemic inflammation and kidney damage
  - liver processes gut-derived metabolites → further effects on kidney
  - liver also secretes molecules that influence gut microbiota and barrier integrity

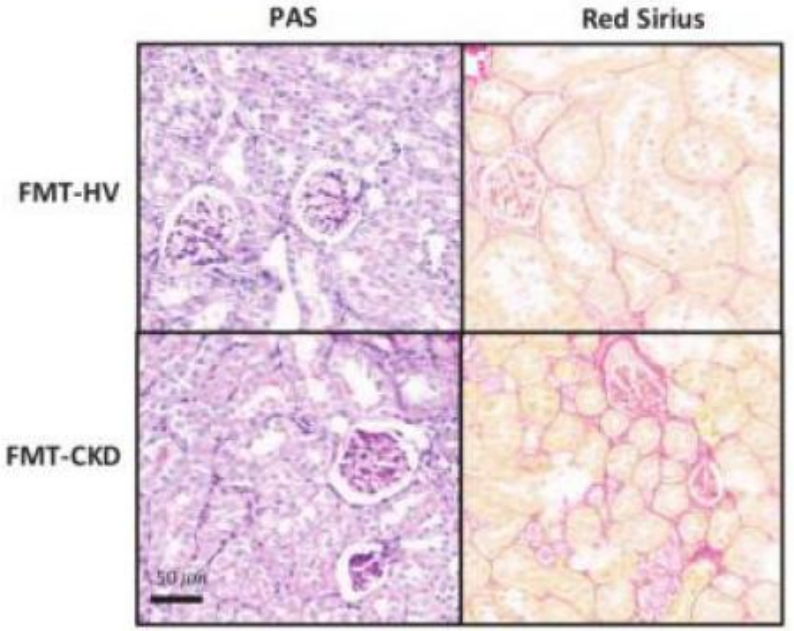
Cyrielle Caussy. CJASN 20: 1626–1629, 2025

Microbiome contribution to metabolome

- 2 CKD cohorts and 1 healthy cohort



FMT from patients with CKD to antibiotic-treated CKD model mice increased serum UT levels and exacerbated kidney fibrosis.



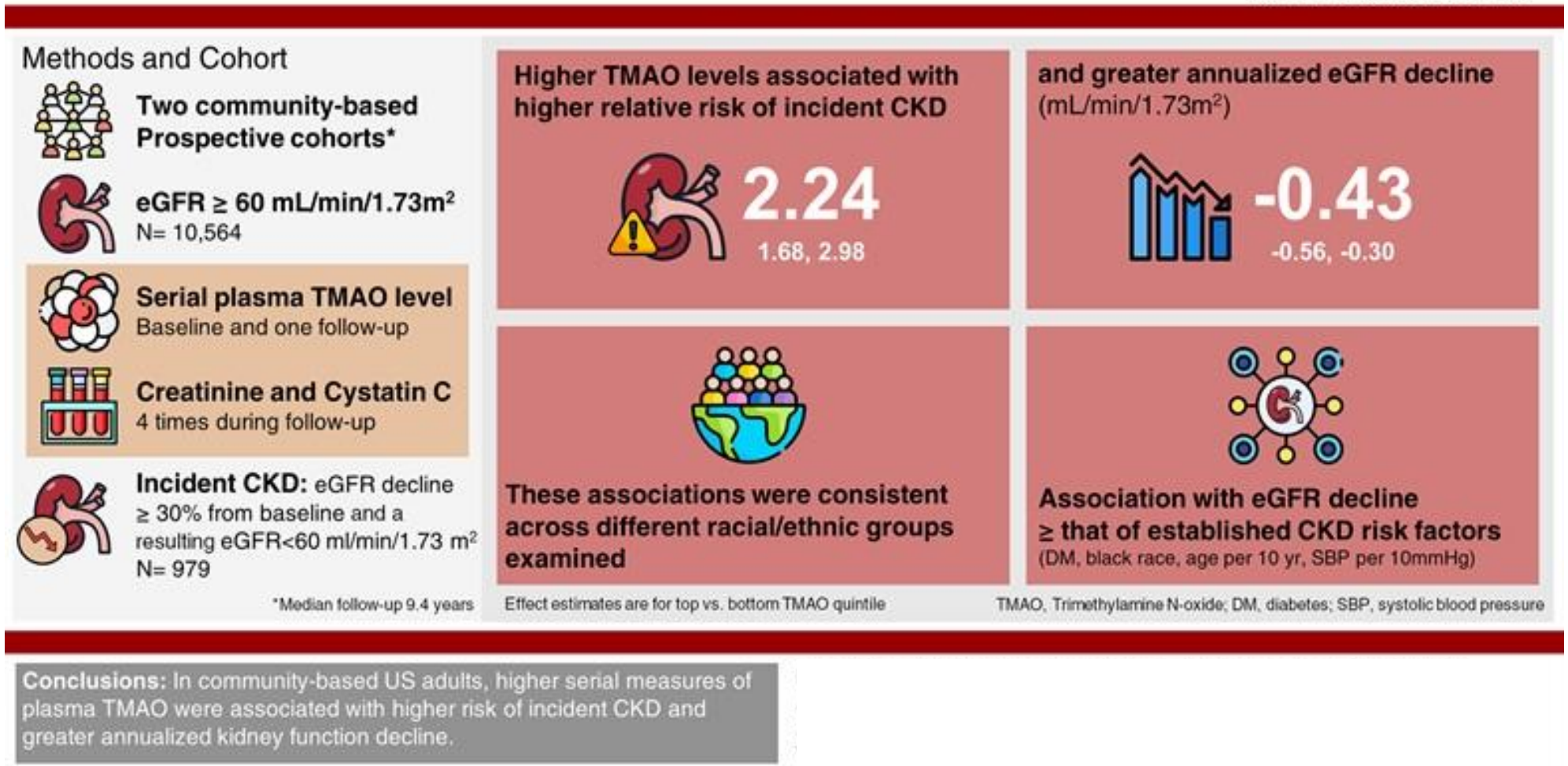
Laiola M. Gut. 2025 Sep 8;74(10):1624-1637.

Uremic toxins and microbiota-derived metabolites tested

Compound	Origin	Role in diseases
TMAO	metabolic product of ingested meat	association with proteinuria, CKD decline, all-cause mortality and CVD
kynurenine	metabolite of tryptophan	increased production associated with worsen depressive symptoms and cognitive dysfunction
kynurenic acid	metabolite of tryptophan	antagonist of glutamate receptors and NMDA receptor; affect synaptic function
hippuric acid	formed from gut microbiota; also produced in the liver and kidneys	a marker for Parkinson's disease
phenyl-acetyl-glutamine	metabolite of phenylacetate in the liver; also produced by gut microbiota	possible marker for cardiovascular disease
indoxyl sulfate	metabolite of tryptophan from gut microbiota	stimulates glomerular sclerosis and renal interstitial fibrosis; contribute to CKD progression; also a predictor of CVD
p-cresyl sulfate	metabolite of aromatic amino acids from gut microbiota	contribute to CKD progression
p-cresyl glucuronide	metabolite of aromatic amino acids from gut microbiota	none reported
indole-3-acetic acid	plant hormone, also produced by some bacterial species	developmental toxicity and immunotoxin in animals
CMPF	endogenous metabolite of furan fatty acids in diet; also produced from gut microbiota	may induce kidney cell apoptosis or ferroptosis

Szeto CC, Ng JKC. Gut. 2025 Jun 5:gutjnl-2025-335600.

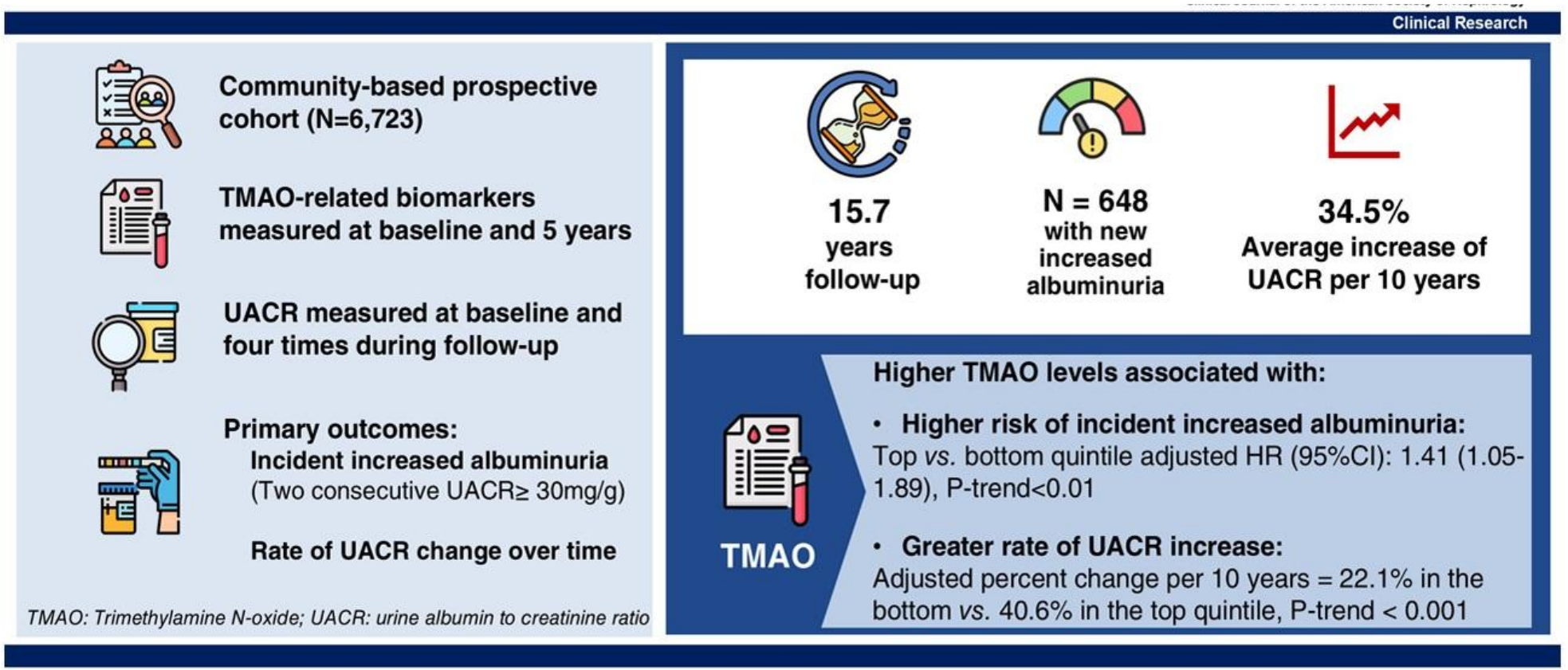
TMAO and kidney function decline



Conclusions: In community-based US adults, higher serial measures of plasma TMAO were associated with higher risk of incident CKD and greater annualized kidney function decline.

Meng Wang. J Am Soc Nephrol June 2024; 35:749

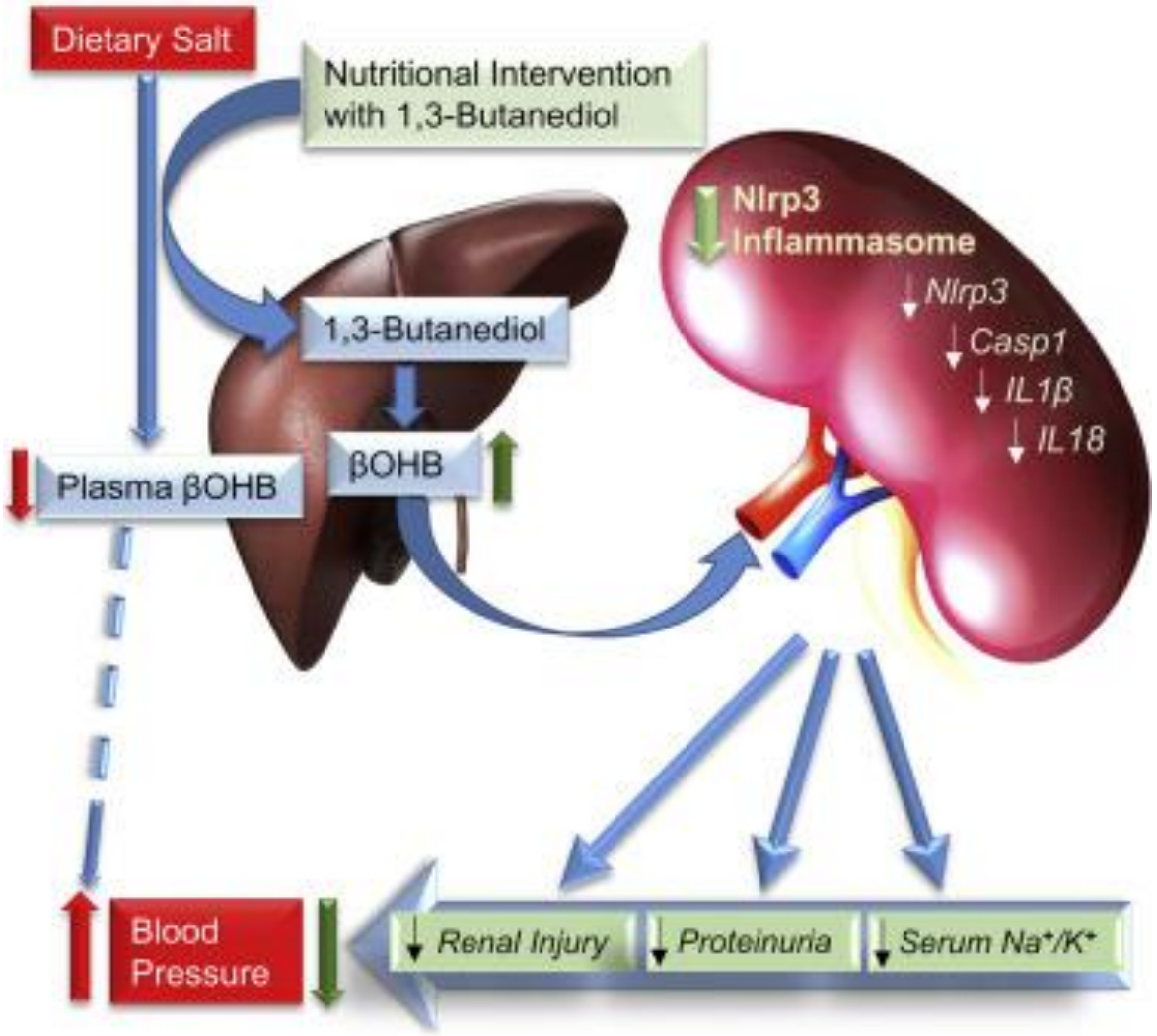
TMAO and albuminuria



Conclusions: TMAO-related gut microbial metabolites appears to be a novel risk factor for albuminuria and its progression, raising the need to investigate the role of targeting the TMAO pathway on albuminuria.

Wang M. Clin J Am Soc Nephrol. 2025 Nov 1;20(11):1549-1563.

Mechanistic exploration: β-hydroxybutyrate and BP



Short term

βHB

↓

SK_{Ca} and IK_{Ca} and Na^+/K^+-ATPase

↓

↑Hyperpolarization

↓

Vasodilation and reduced vascular load

Long term

βHB

↓

↑NO bioavailability

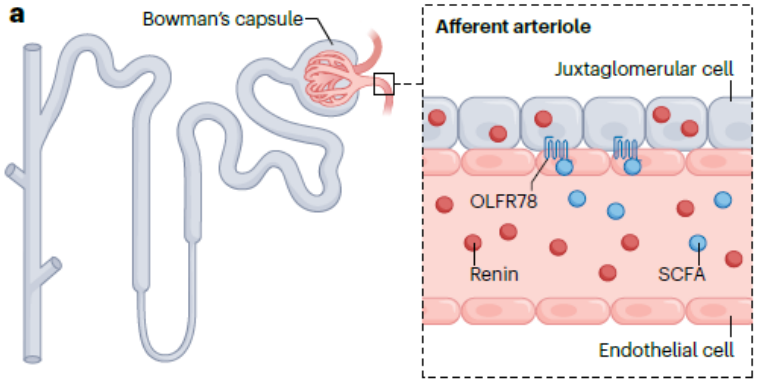
↓

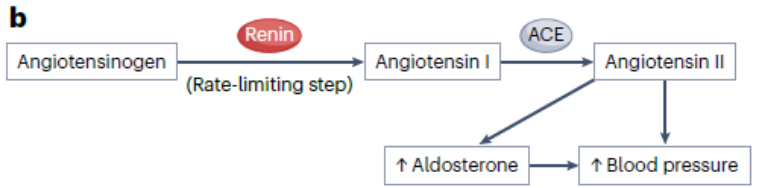
↓Hypertension

Chakraborty S.
Cell Rep. 2018 Oct 16;25(3):677-689.e4.

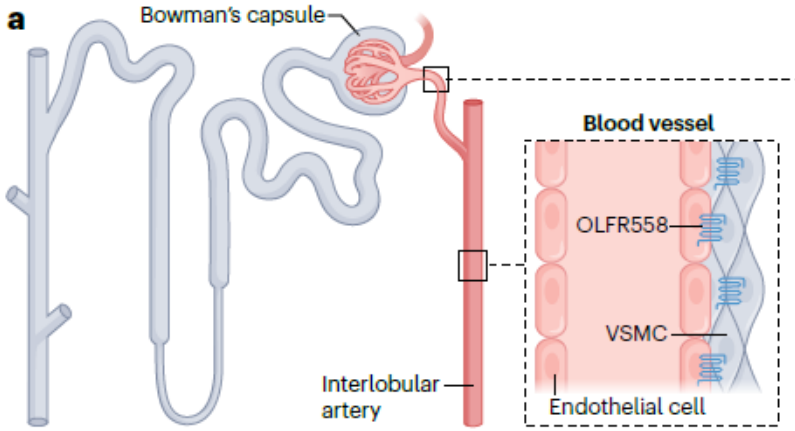
Can the kidney sense specific metabolites?

OLFR78 for acetate and propionate regular renin synthesis

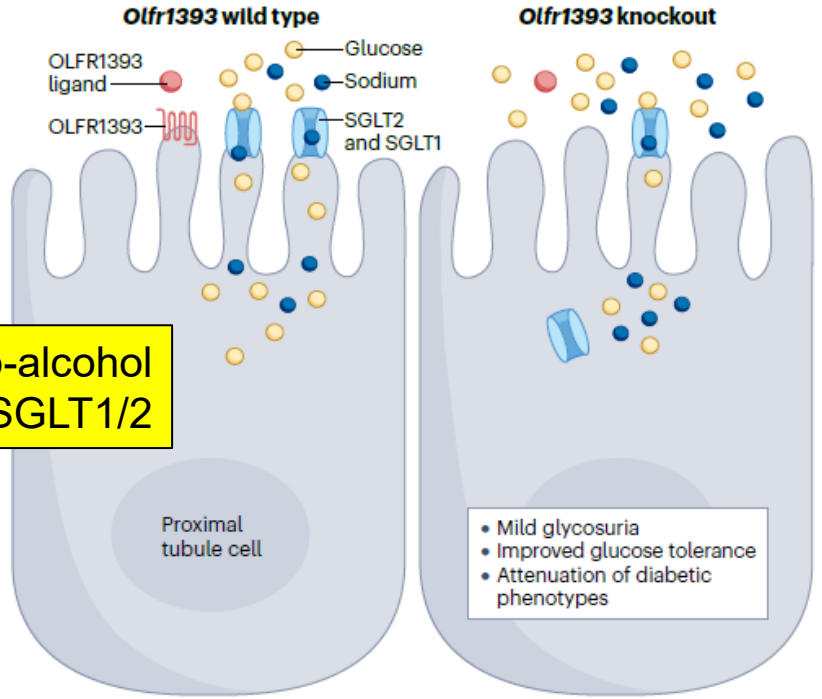




sense by smelling !?



OLFR558 for butyric acid regular afferent arteriole tone



OLFR1393 for keto-alcohol interact with SGLT1/2

Xu J. Nat Rev Nephrol. 2025 Apr;21(4):253-263.

Conclusion

- advance in methodologies
- metabolomic changes are context and cell-type specific
- contribution of gut microbiota to metabolomic alterations
- kidney can “sense” many metabolites at low concentrations