The influence of chronic kidney disease on gut microbial metabolism

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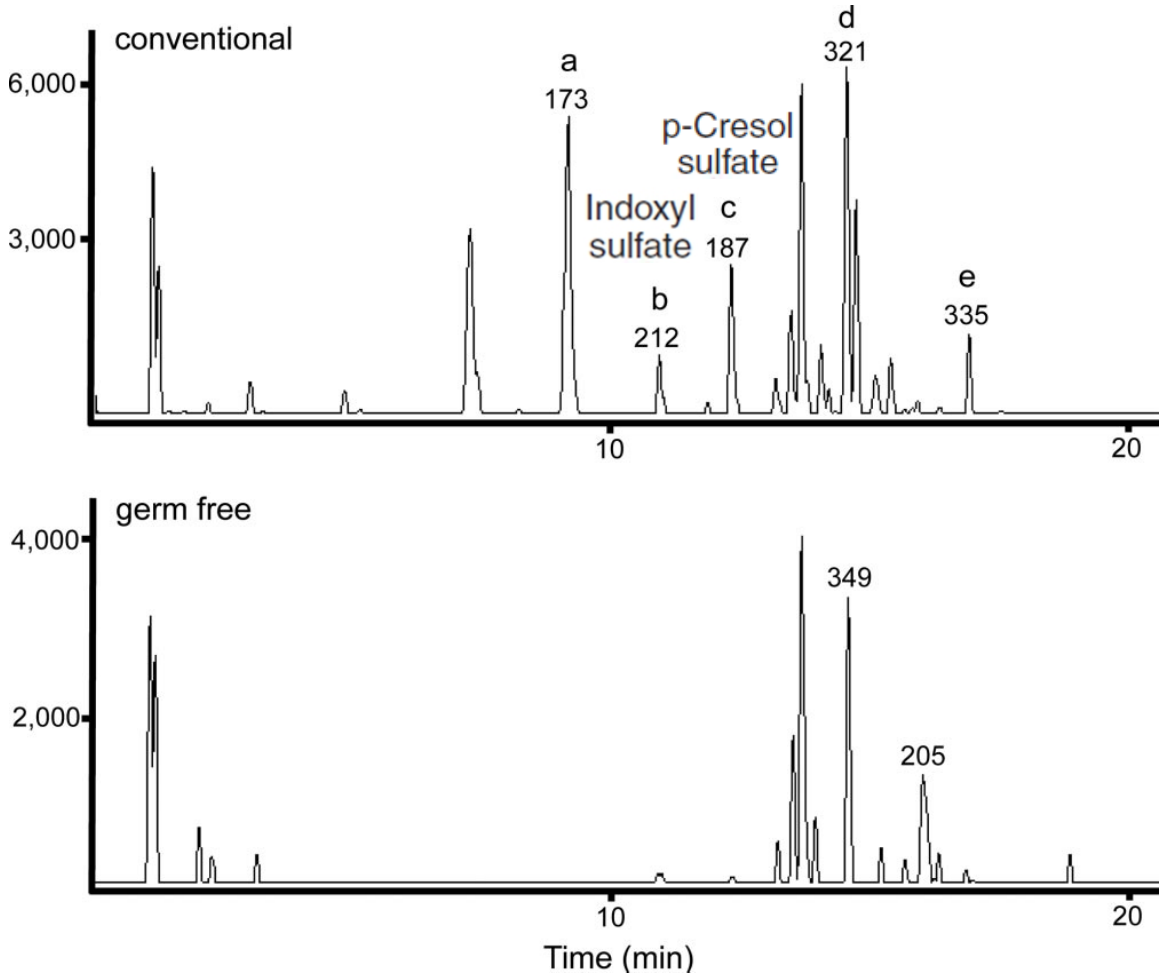
Gut microbiome vs. mammalian metabolome

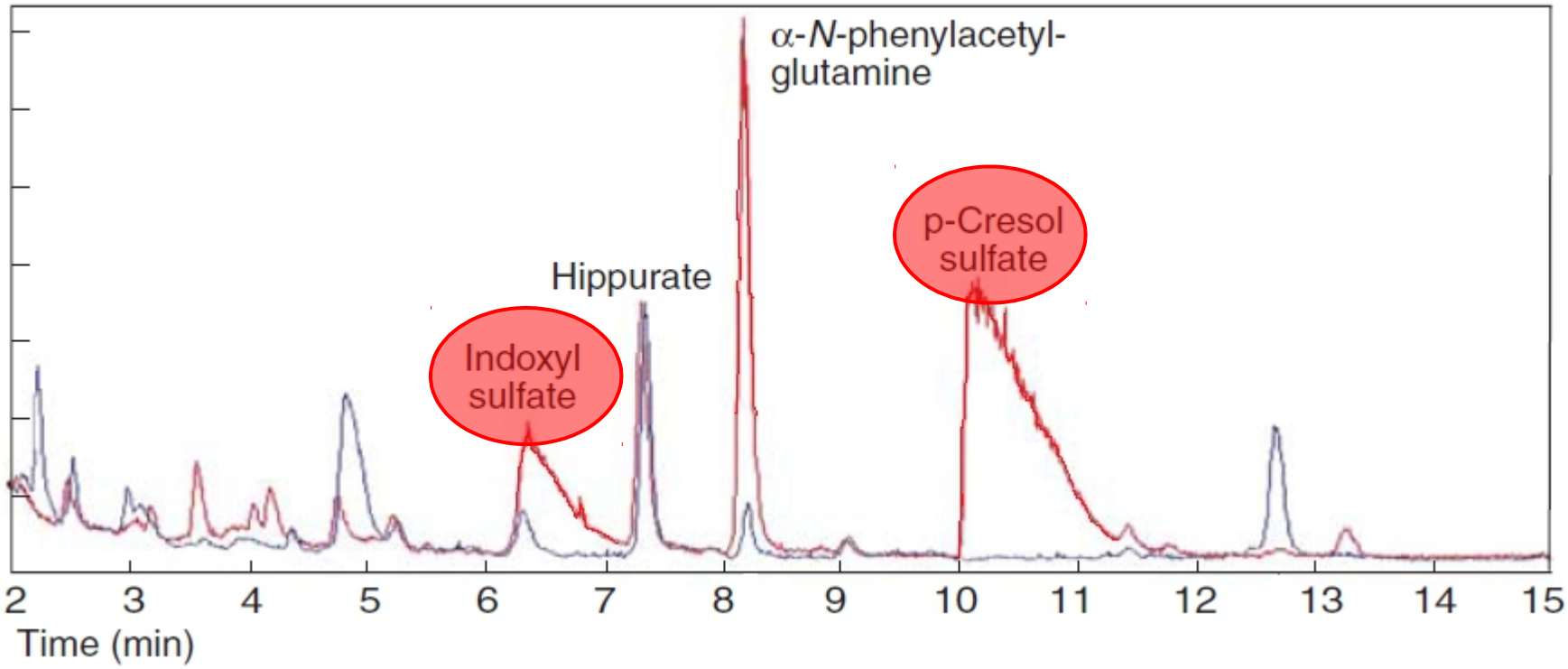


Conventional mice

Germ-free mice

Wikoff et al. Proc Natl Acad Sci U S A. 2009 ;106(10):3698-703

Colon-derived uremic retention solutes



Hemodialysis patient with intact colon

vs.

Hemodialysis patient with colectomy

Meyer et al. Kidney Int. 2012;81:949-54

Aronov et al. J Am Soc Nephrol. 2011;22:1769-76

Colon-derived uremic retention solutes

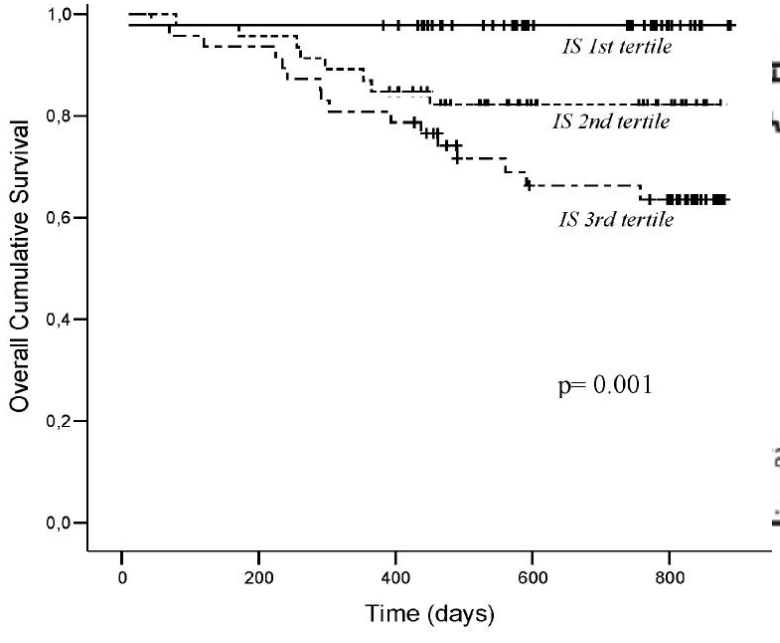
Indoxyl sulfate

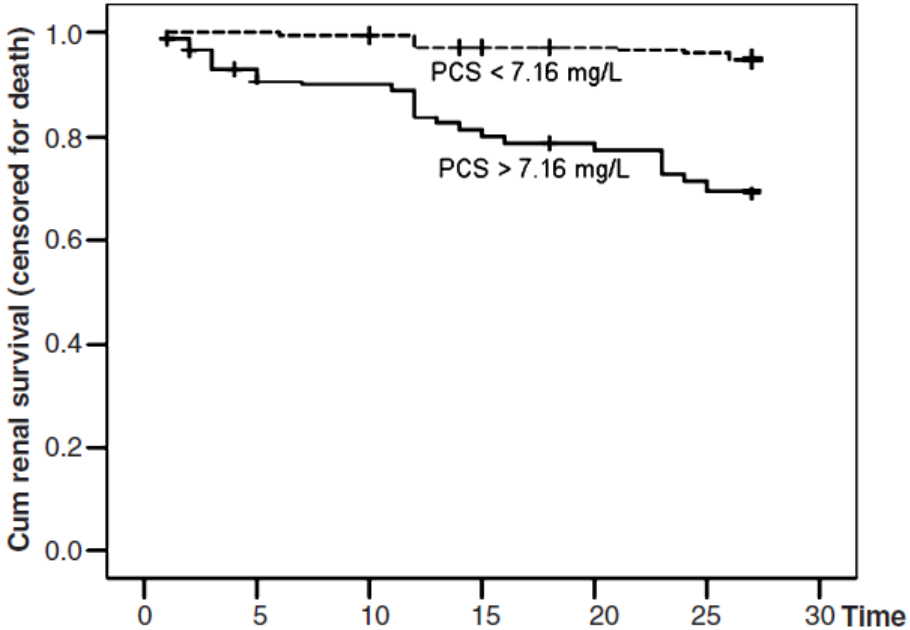
p-Cresol sulfate

Overall survival

Cardiovascular disease

CKD progression





Barreto et al. Clin J Am Soc Nephrol. 2009;4(10):1551-1558

Meijers et al. Clin J Am Soc Nephrol. 2010;5(7):1182-1189

Wu et al. Nephrol Dial Transplant. 2011;26(3):938-947

The gut microbiota and CKD

- CKD changes the gastro-intestinal environment

  diet, drug therapy, colonic transit time, pH, intraluminal urea/ammonia, small intestine protein assimilation, …

- Gut microbiota: disease-related?

  → obesity, IBD, diabetes mellitus, …

  → **“CKD alters microbial flora”**

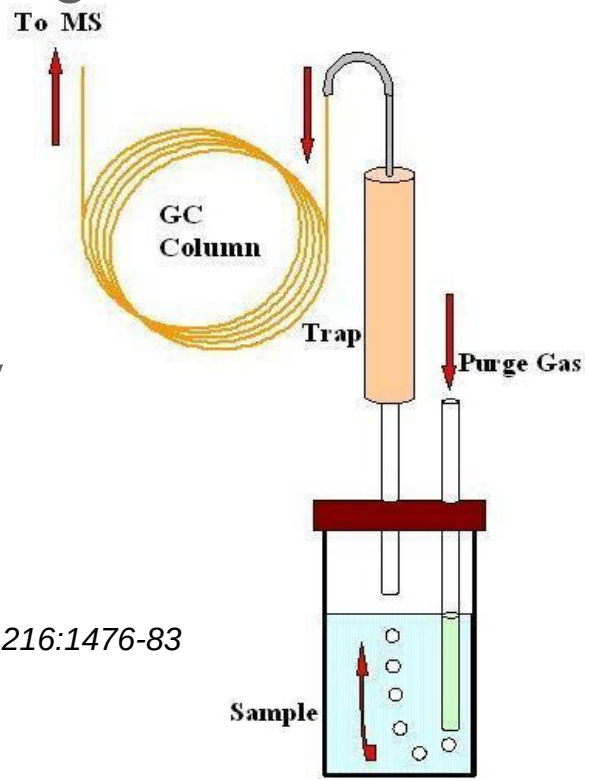
Vaziri et al. Kidney Int. 2013;83:308-15

- Impact of CKD on gut **microbial metabolism**?

Methodology

- Collection of fecal samples of hemodialysis patients (HD) and healthy controls

- Untargeted fecal metabolic fingerprinting
  - → Volatile organic compounds
    (including *p*-cresol and indole)
  - → Purge-and-trap system
  - → Gas chromatography-mass spectrometry
    (GC-MS)

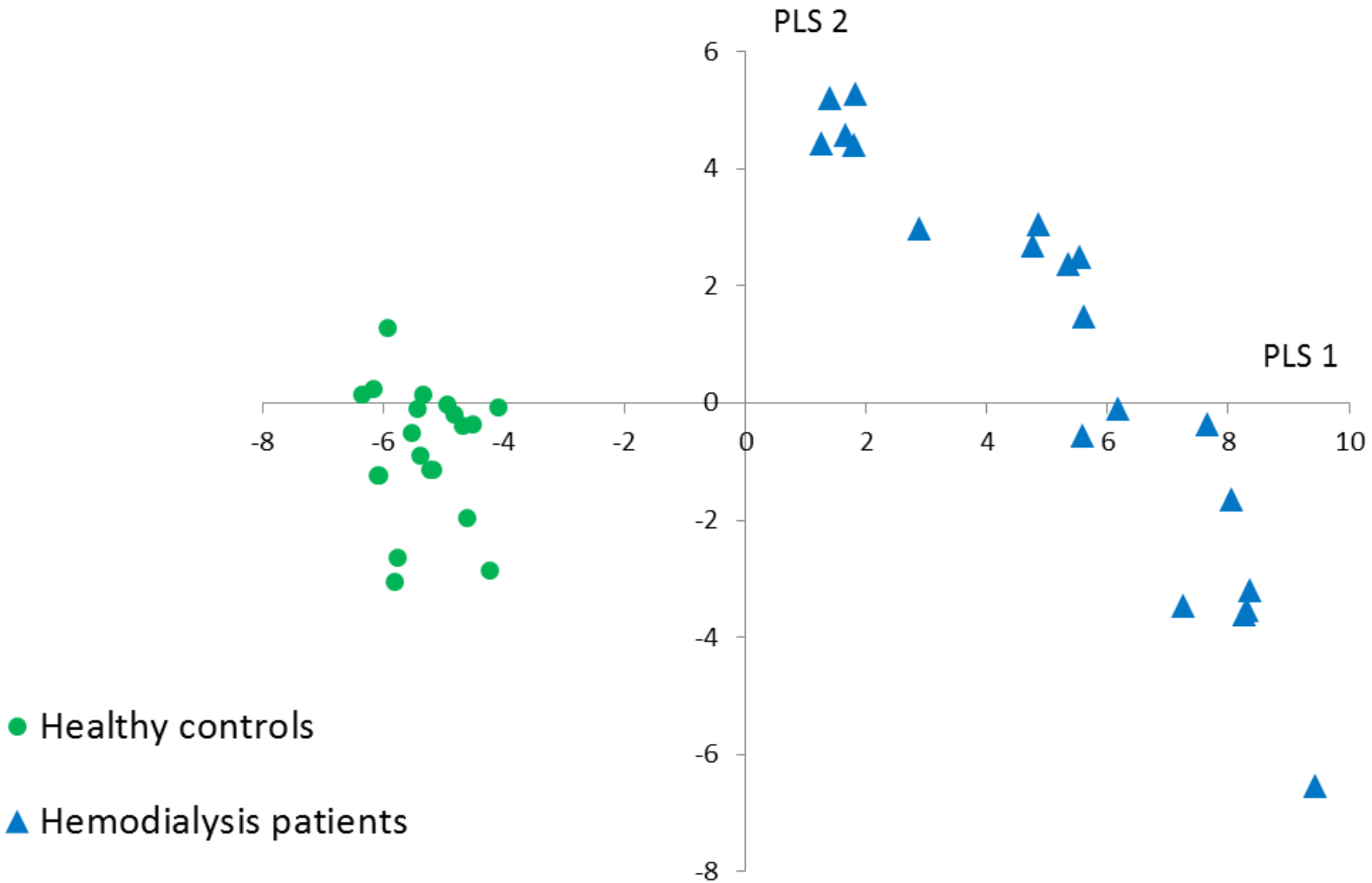


De Preter et al. J Chromatogr A. 2009;1216:1476-83

Statistical analysis

- Clustering of samples?
  - PLS-DA
- Discriminating volatile organic compounds?
  - Correlation loading plot
  - Wilcoxon rank-sum
  - Multi-comparison with Benjamini-Hochberg FDR

Results


PLS 2
PLS 1
6
4
2
0
-2
-4
-6
-8
-8
-6
-4
-2
0
2
4
6
8
10
Healthy controls
Hemodialysis patients

Results

- Discriminating individual metabolites?

92 volatile organic compounds (FDR adjusted)

60 upregulated

→ *p*-cresol (precursor of *p*-cresyl sulfate) ↑

→ indole (precursor of indoxyl sulfate) ↑

32 downregulated

- Discriminating chemical classes (loading plot – wilcoxon)?

upregulated: Alcohols, aldehydes, benzenes, BCFA, furans, indoles

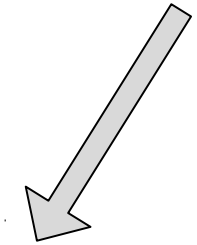
downregulated: Alka/enes, ketones

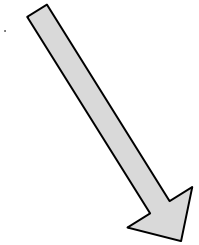
Renal phenotype vs. uremia?

- Discrimination of fecal metabolite profiles of HD patients and healthy controls
- Difference due to

  renal phenotype vs. uremia?

Diet
Drug therapy
Age
Co-morbidity
(e.g. diabetes mellitus)





HD patients vs.

healthy controls

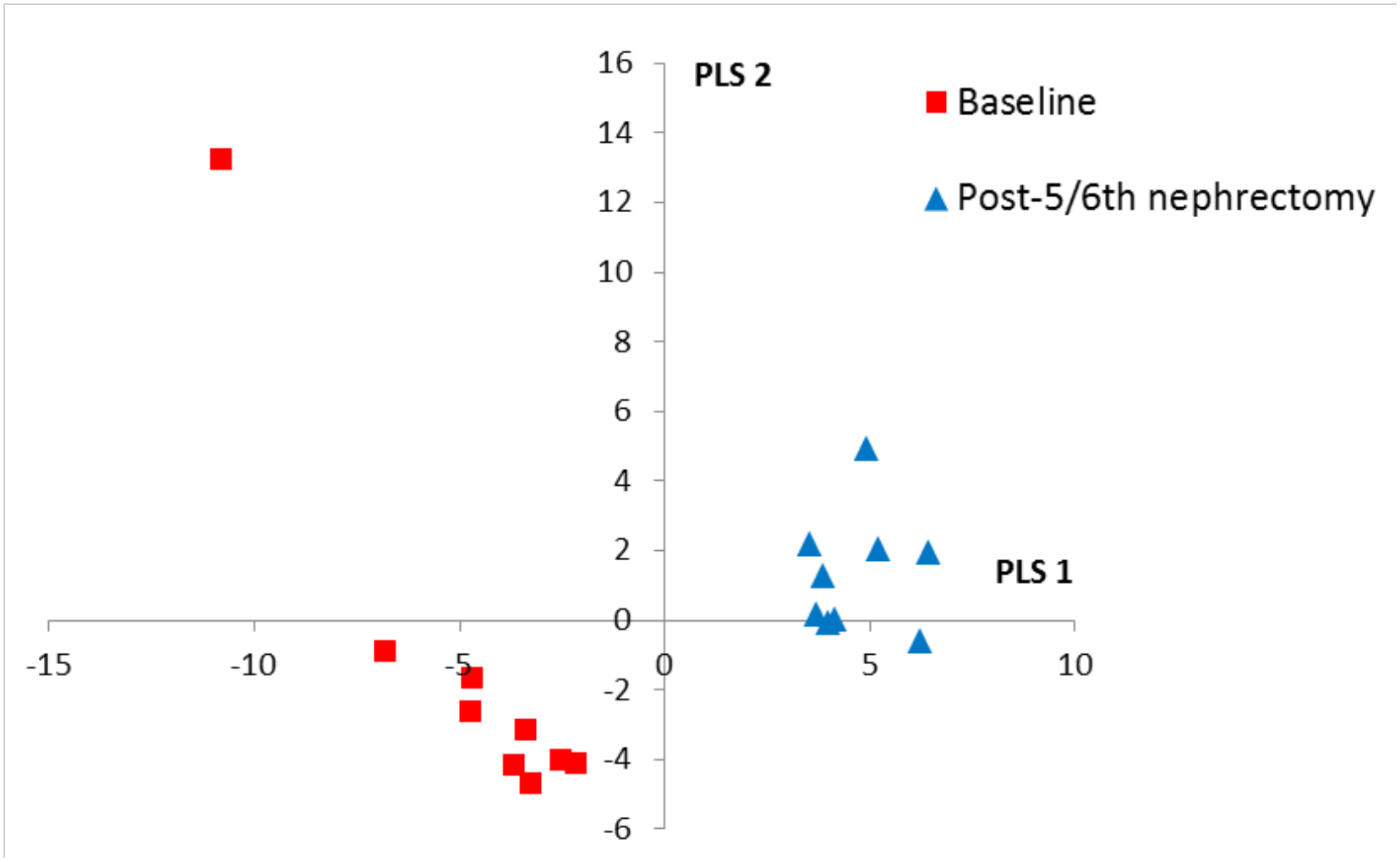
Rats at baseline vs.

post-5/6th nephrectomy **on same diet**

HD patients vs.

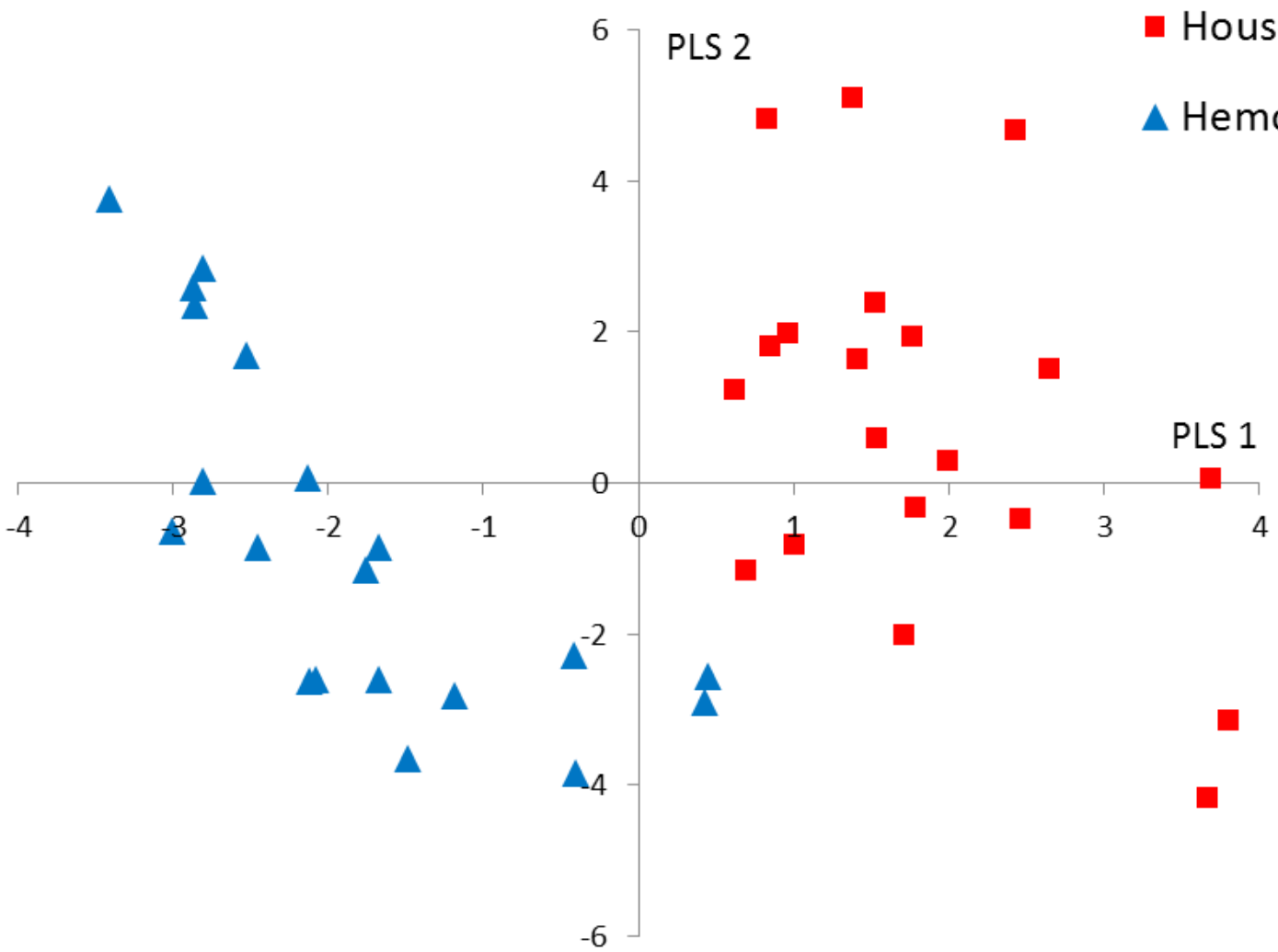
household contacts **on same diet**

Influence of uremia



Rats at baseline vs. post-5/6th nephrectomy **on same "normal" diet**

Influence of uremia

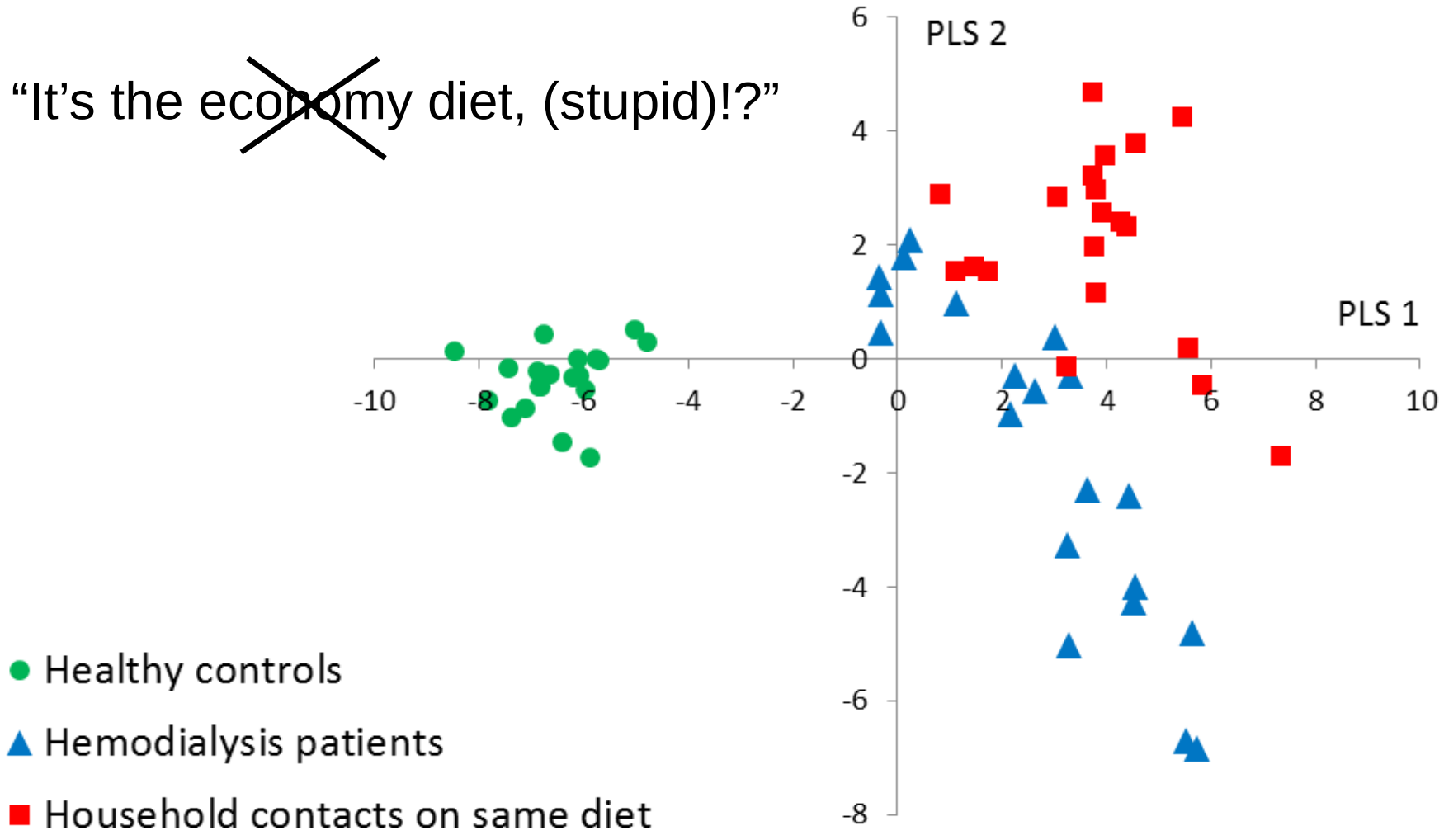


+ no difference in:
- age
- gender
- BMI
- diabetes

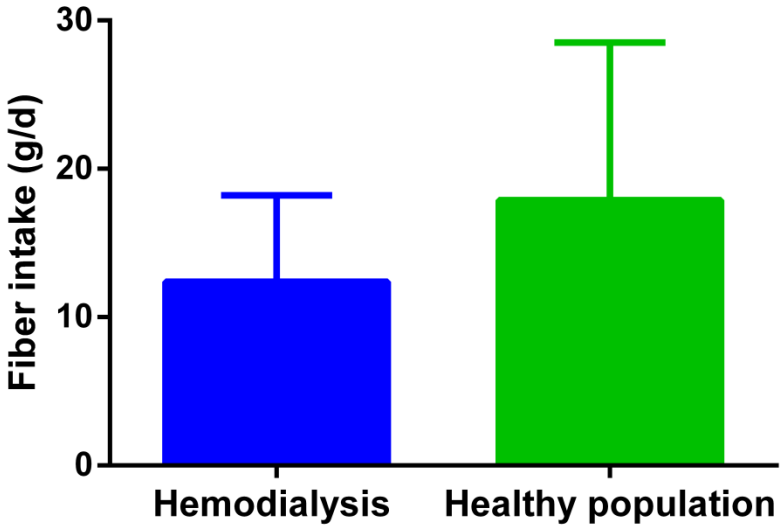
HD patients vs. household contacts **on same "renal' diet**

Renal phenotype vs. uremia

"It's the ~~economy~~ diet, (stupid)!?"



Healthy vs. renal diet?



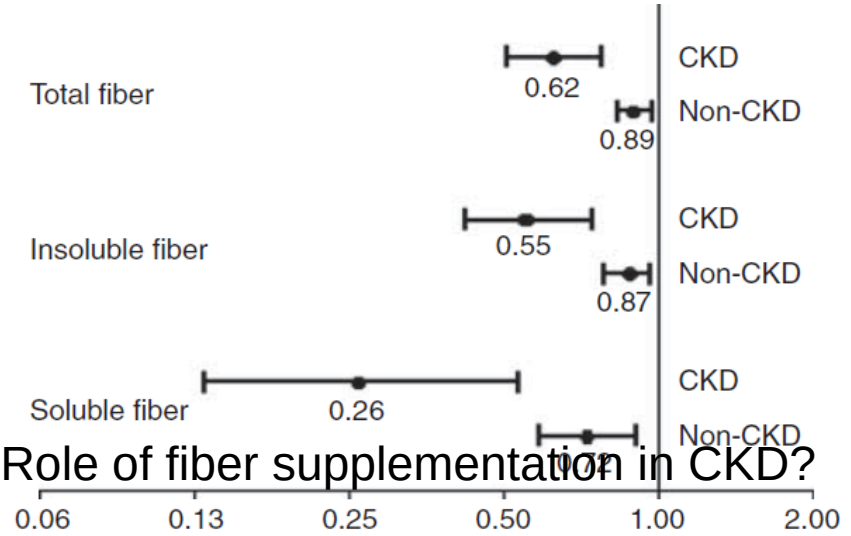
***P* 0.02**

Adapted from Kalantar-Zadeh et al. J Ren Nutr. 2002;12:17-31

Significantly less fiber intake in advanced CKD due to dietary restrictions!

Healthy vs. renal diet?

Higher fiber intake
=
less inflammation

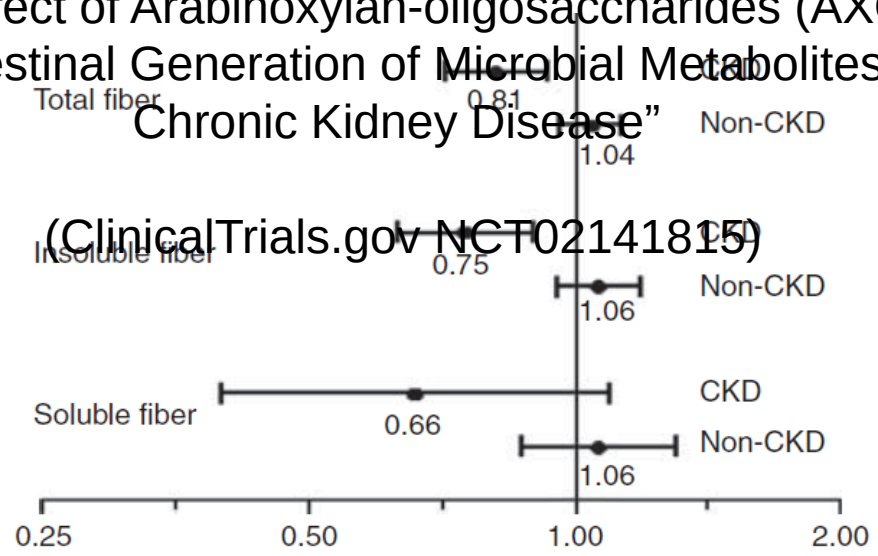


Role of fiber supplementation in CKD?

"The Effect of Arabinoxylan-oligosaccharides (AXOS) on Intestinal Generation of Microbial Metabolites in Chronic Kidney Disease"

(ClinicalTrials.gov NCT02141815)

Higher fiber intake
=
less mortality



Krishnamurthy et al. Kidney Int. 2012 ;81(3):300-306

Conclusions

- The renal phenotype is associated with a distinct gut microbial metabolism
- Increased generation of *p*-cresol and indole in HD patients vs. healthy controls
- Role of renal diet (age, co-morbidity) + uremia

  ⇔ Influence of uremia *per se* is less pronounced
- Impact of therapeutic strategies targeting the gut microbial metabolism needs further investigation