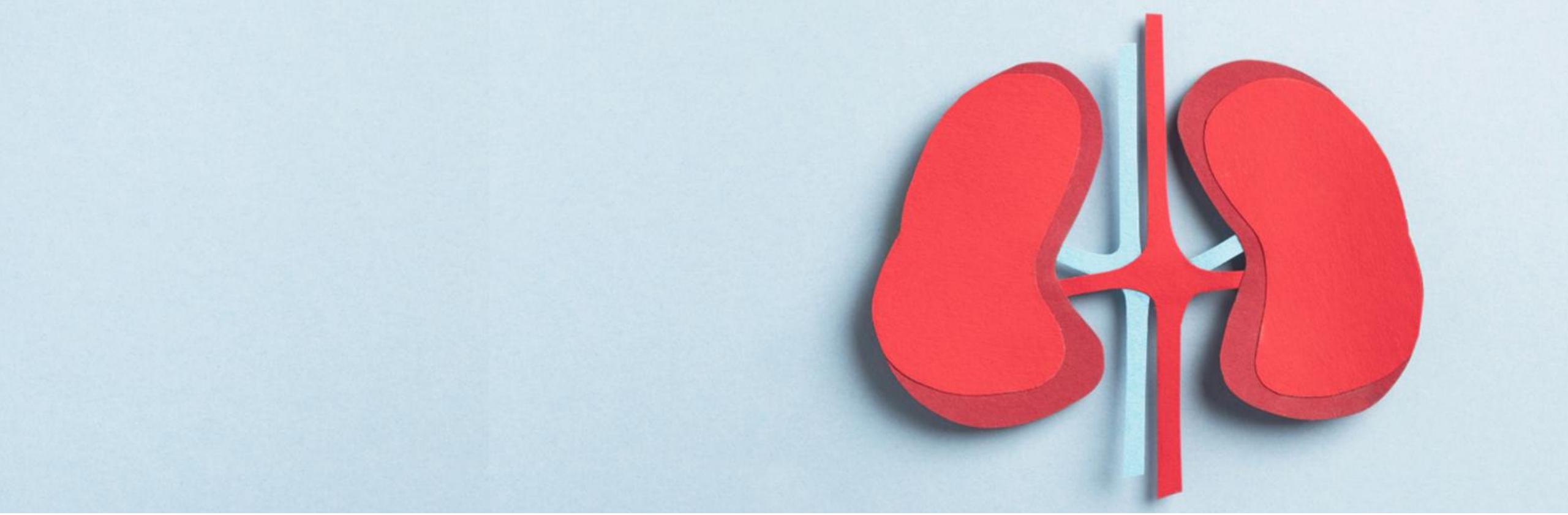


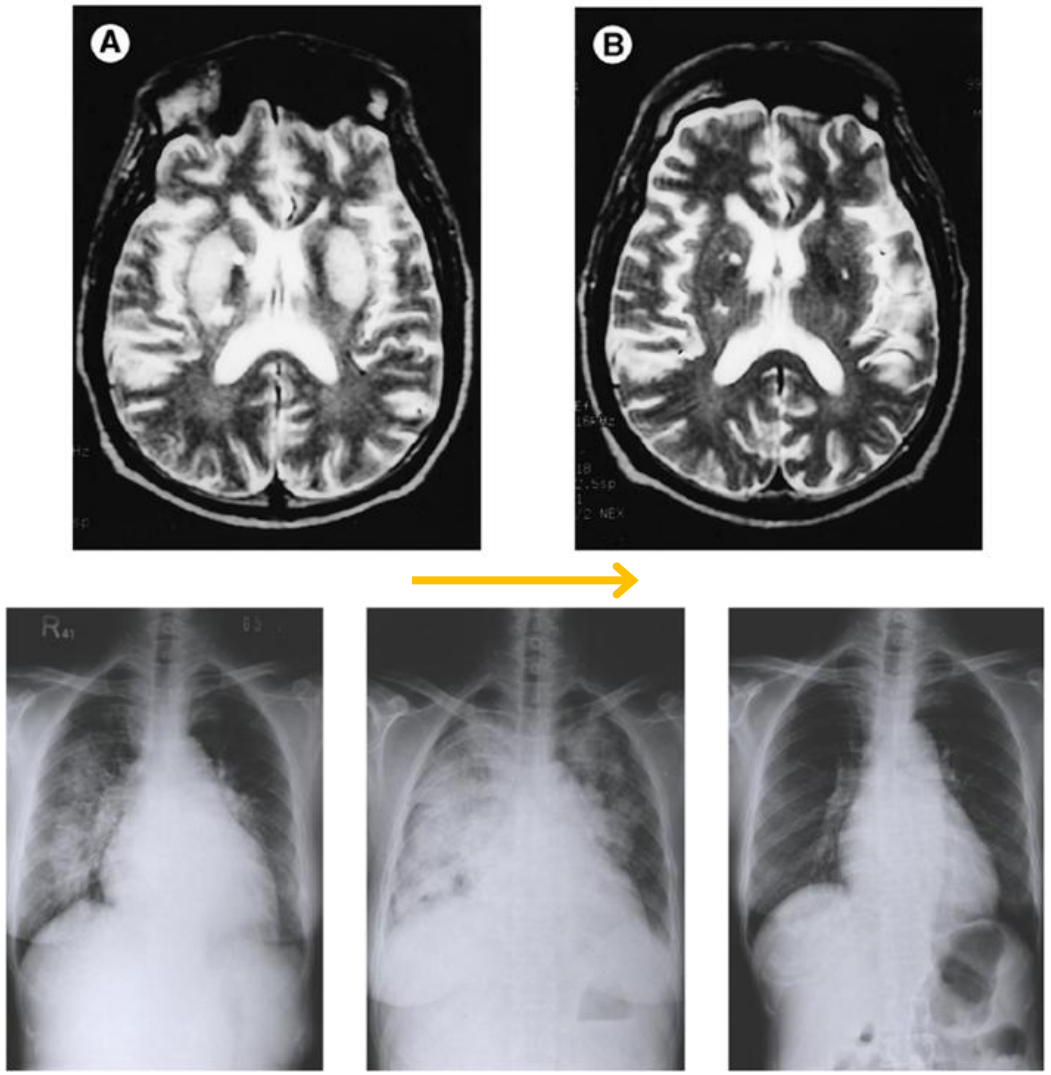
Beyond Calories and Protein Redefining Nutritional Care in CKD

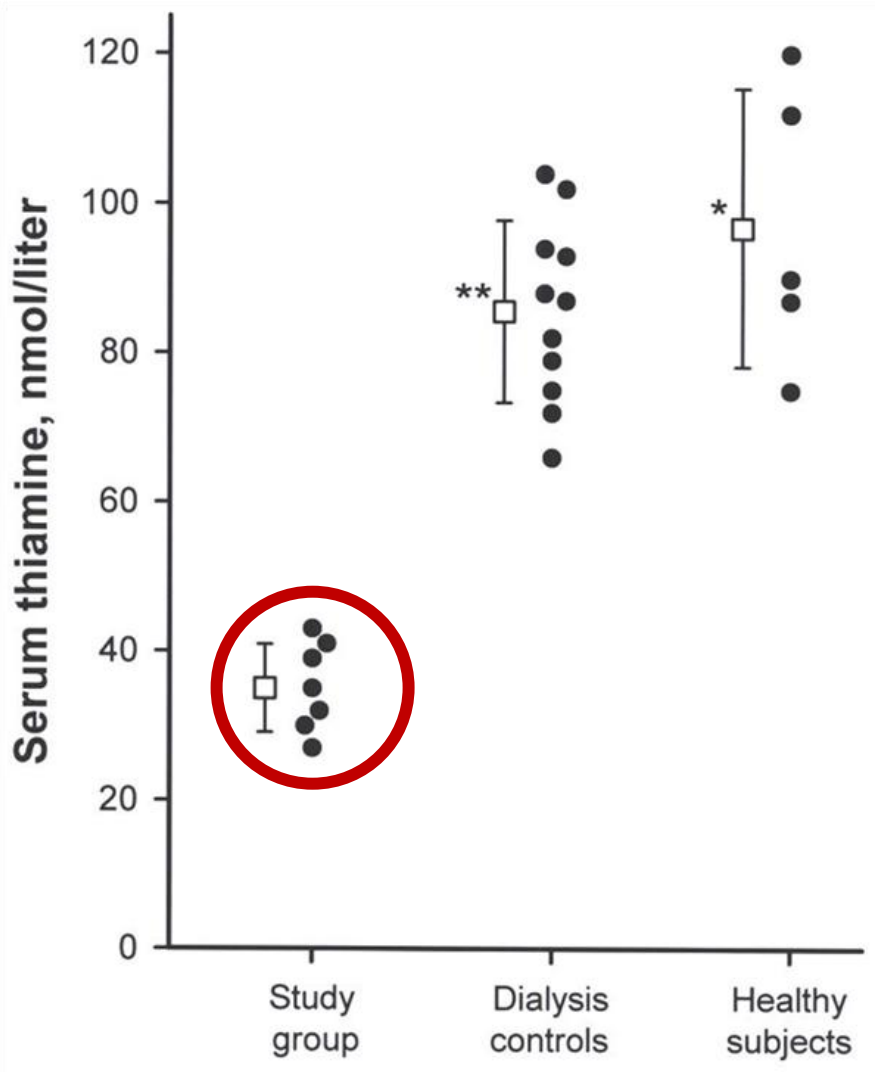
Szu-Chun Hung, MD, FASN

Division of Nephrology, Taipei Tzu Chi Hospital, Taiwan

APCN×TSN 2025

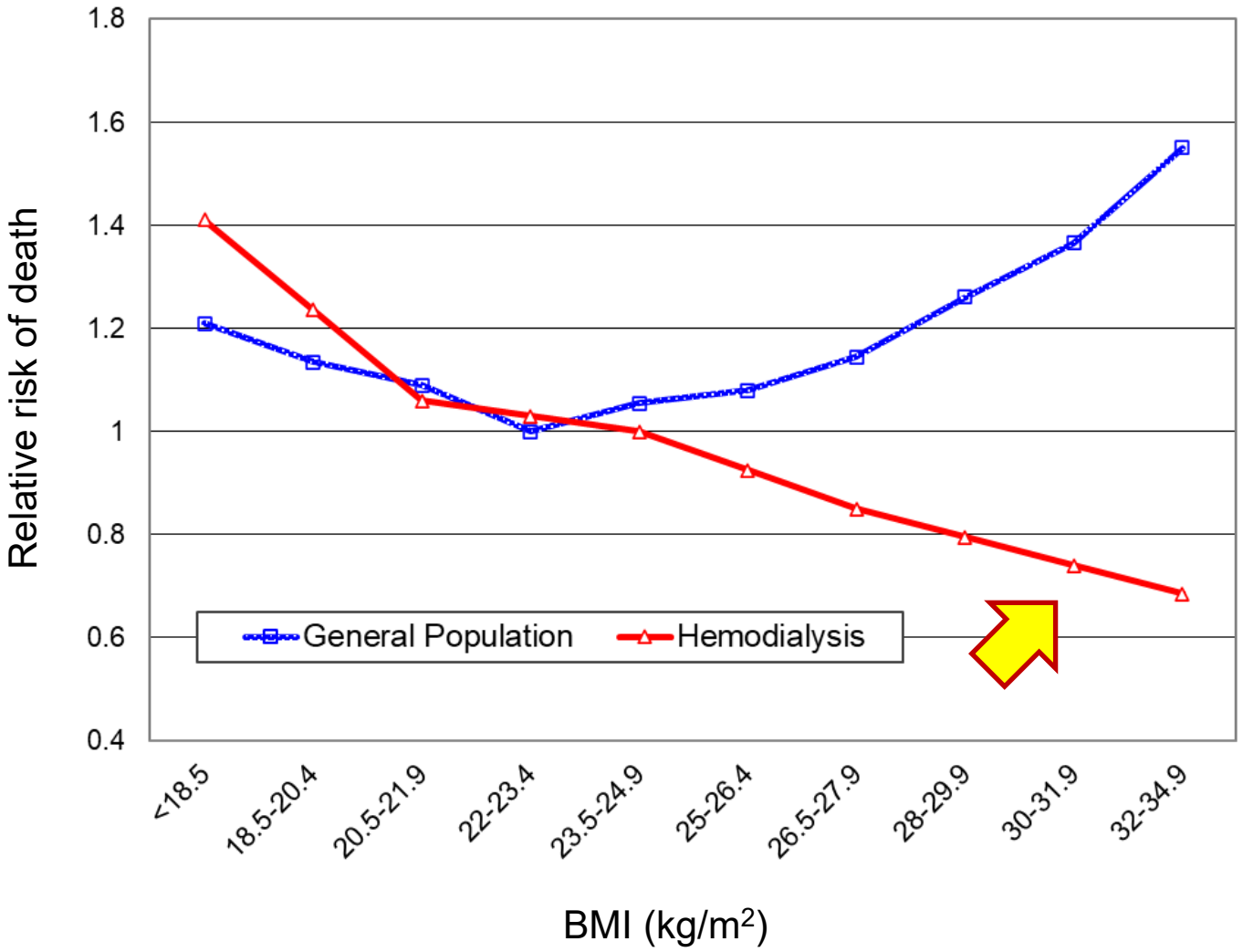
Thiamine Deficiency in HD Patients





Hung SC et al. Am J Kidney Dis 38:941–947, 2001

Reverse Epidemiology of CV Risk Factors in HD Patients



Kamyar Kalantar-Zadeh

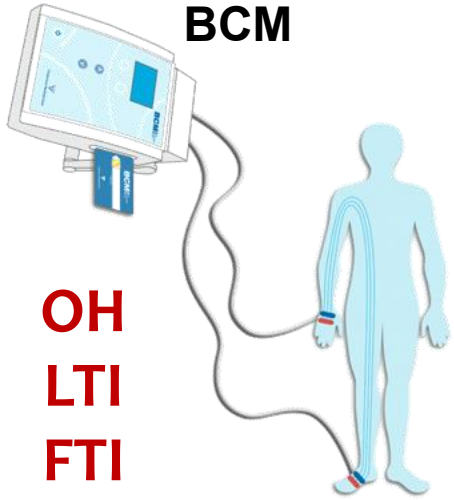
Kalantar-Zadeh K et al. Kidney Int 63:793–808, 2003

Body Composition and Outcomes in CKD

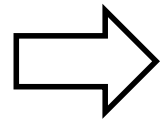
338

CKD 3–5
eGFR 29
Age 66
Males 69%
DM 45%
CVD 24%

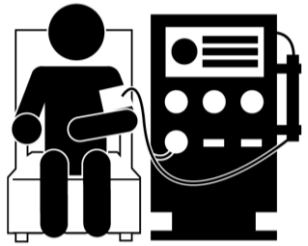
BCM



OH
LTI
FTI



Clinical outcomes



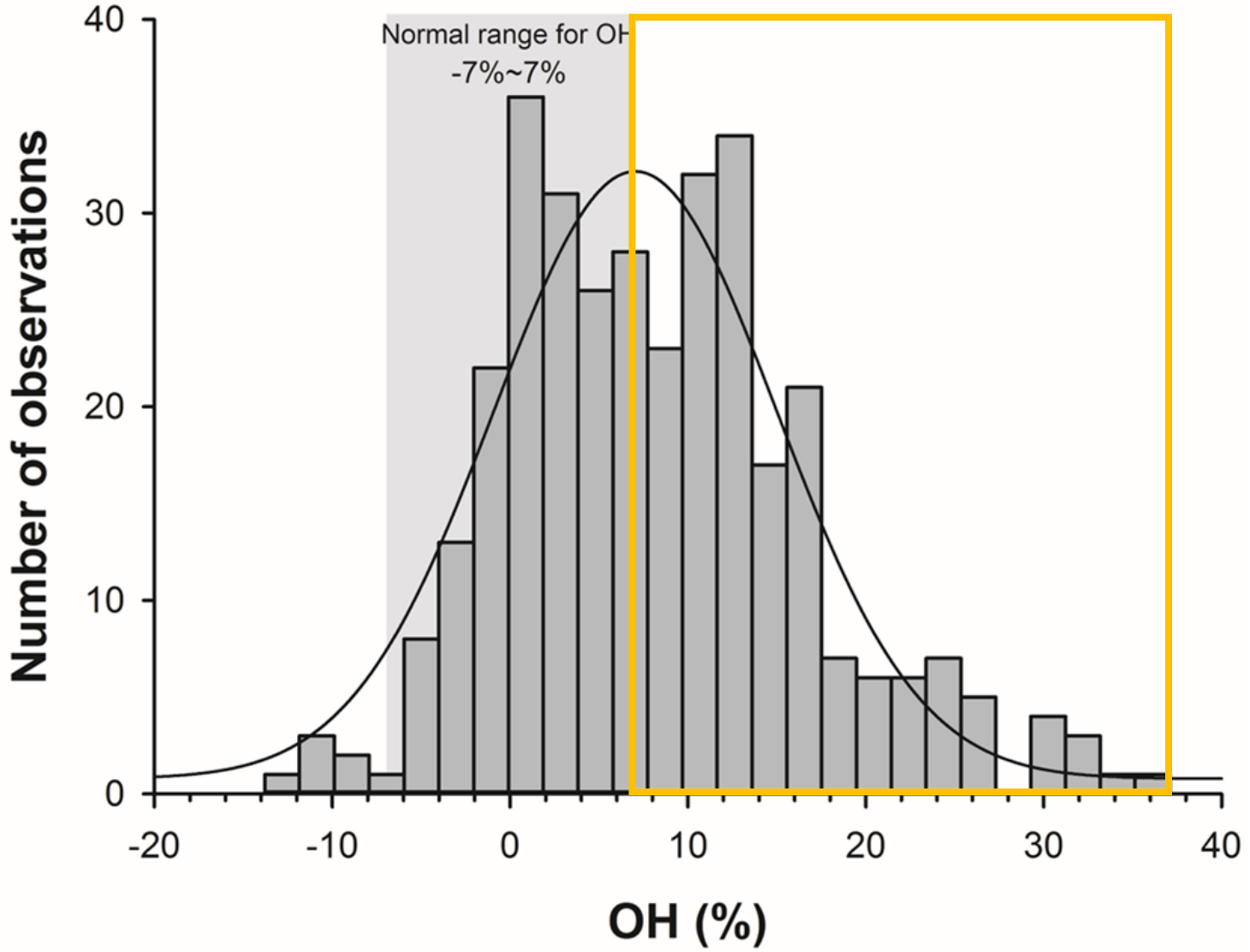
CKD risk factors

CVD risk factors

Nutritional markers

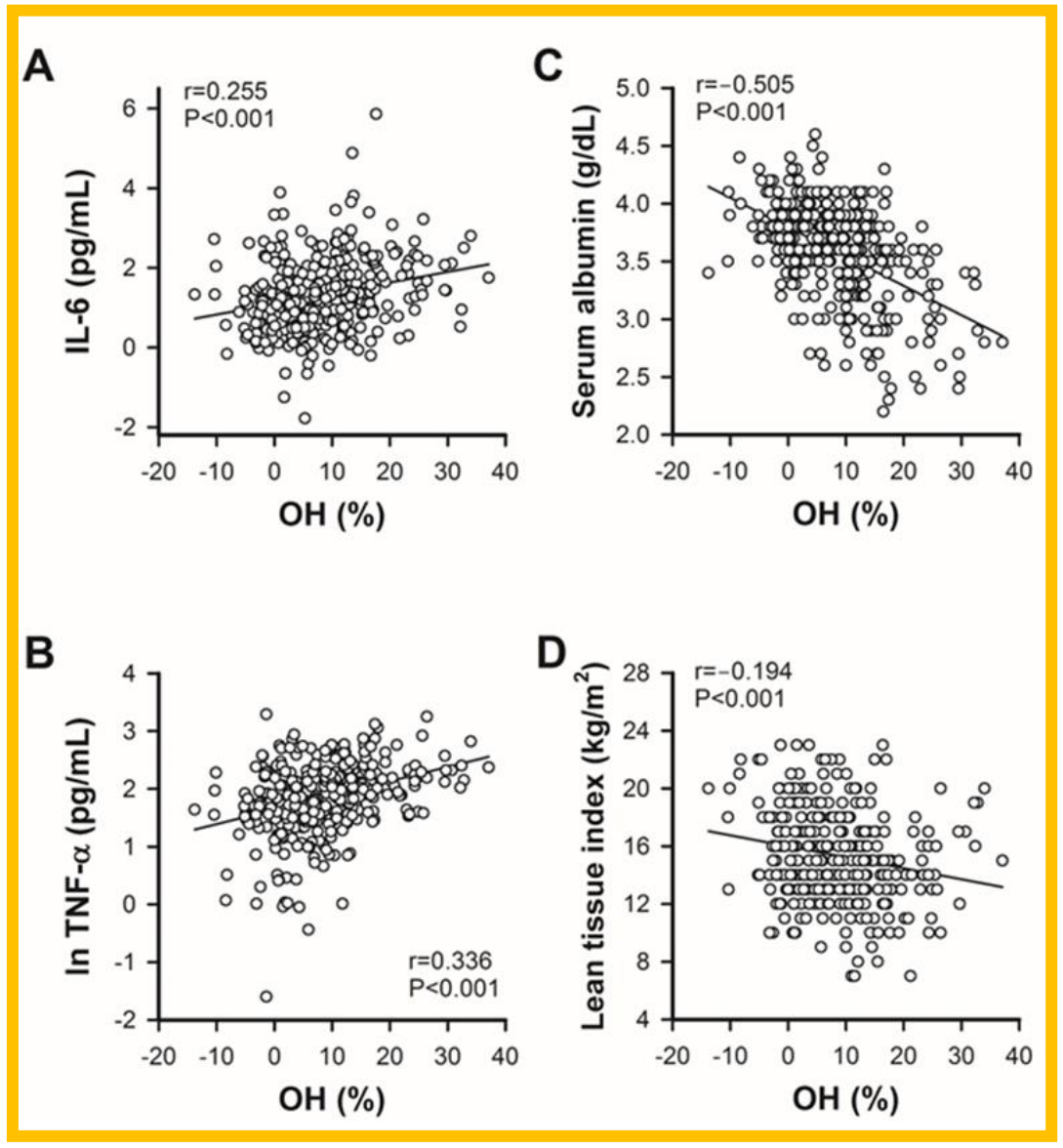
Hung SC et al. Kidney Int 85:703–709, 2014

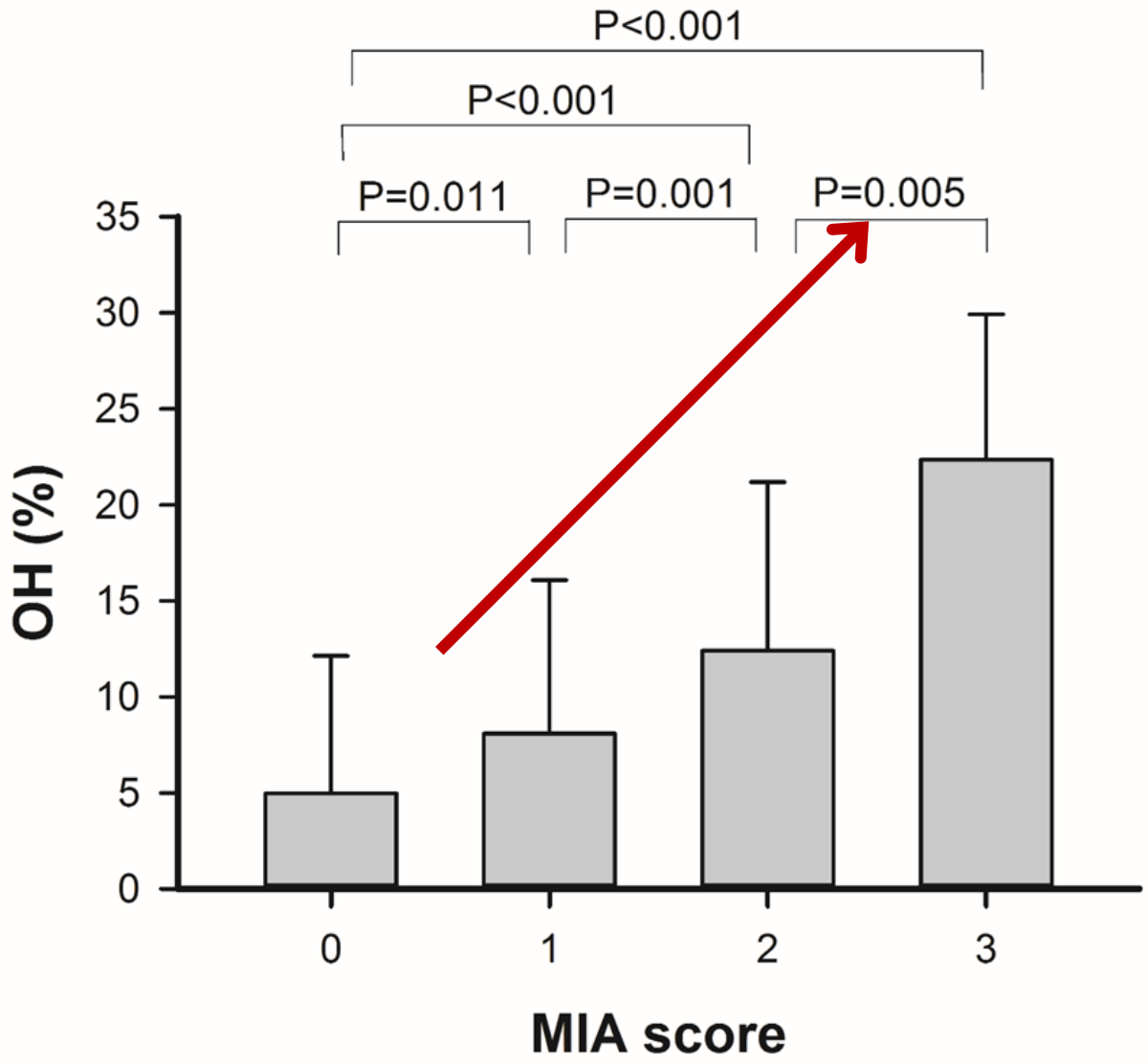
Prevalence of Volume Overload in CKD



Hung SC et al. Kidney Int 85:703–709, 2014

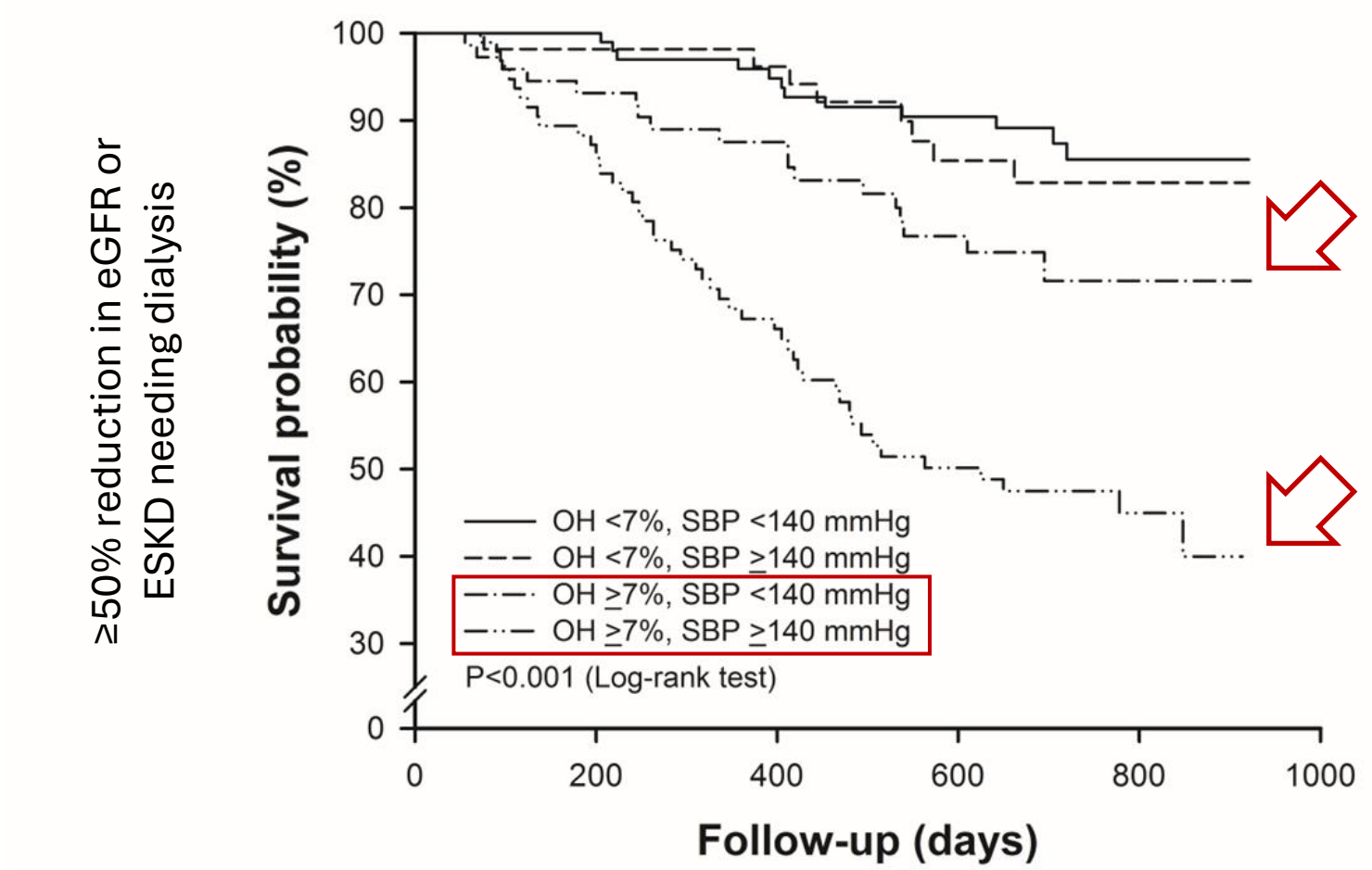
Volume Overload and MIA Syndrome in CKD





Hung SC et al. Kidney Int 85:703–709, 2014

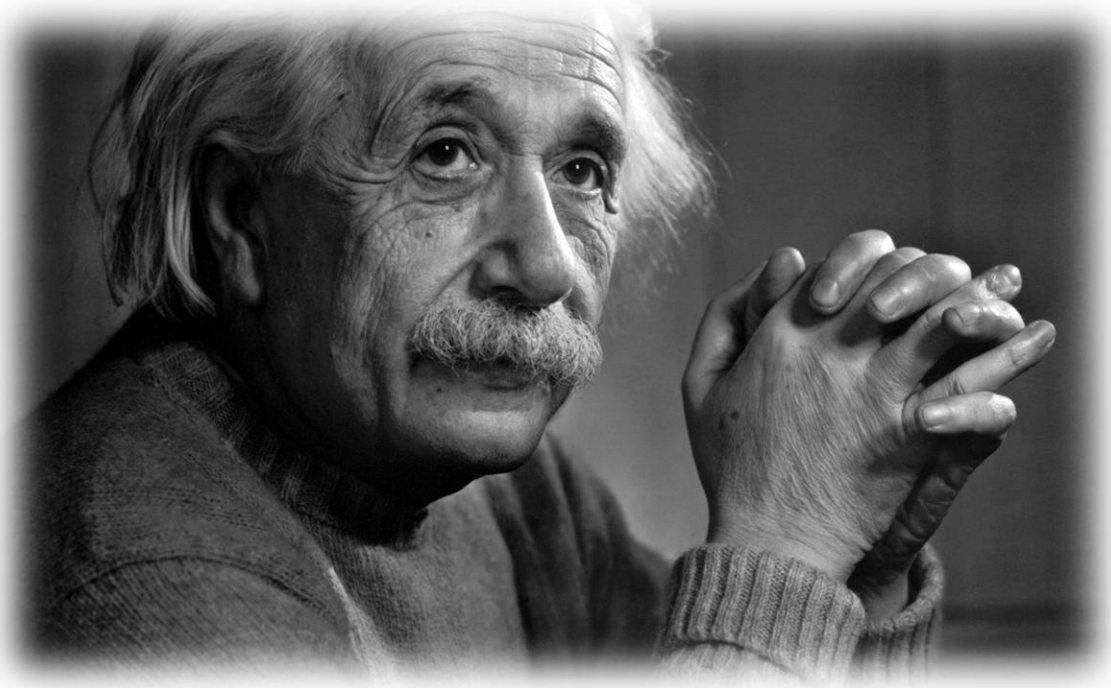
Volume Overload and Clinical Outcomes in CKD



No. at risk					
OH <7%, SBP <140 mmHg:	103	103	88	73	36
OH <7%, SBP ≥140 mmHg:	55	51	48	38	17
OH ≥7%, SBP <140 mmHg:	73	68	60	41	12
OH ≥7%, SBP ≥140 mmHg:	95	79	58	39	15

Hung SC et al. J Am Heart Assoc 4:e001918, 2015

"Not everything that counts can be counted, and not everything that can be counted counts."

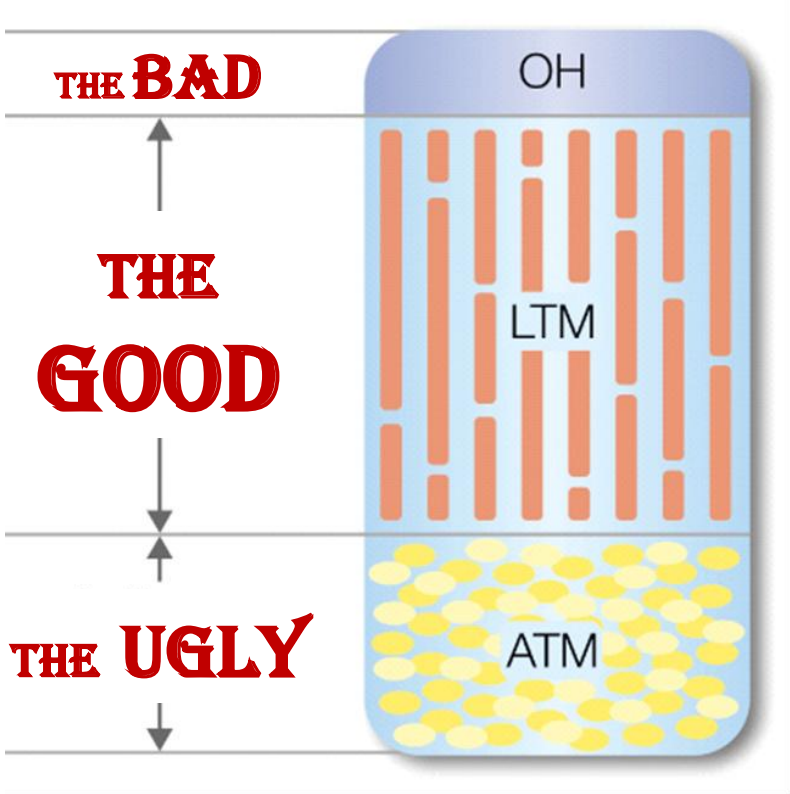


Body Composition and Clinical Outcomes in CKD

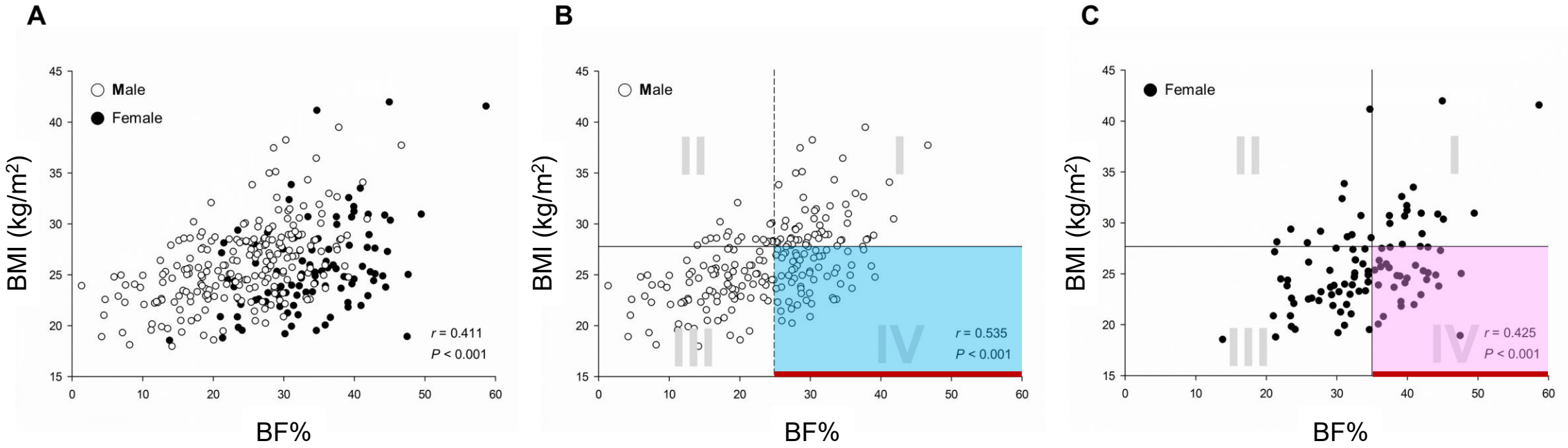
Outcome	Unadjusted		Model 1		Model 2	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
All-cause mortality						
BMI (H vs L)	0.44 (0.23–0.85)	0.014	0.51 (0.26–0.99)	0.047	**0.44 (0.22–0.87)**	**0.019**
FTI (H vs L)	0.98 (0.53–1.82)	0.945	0.69 (0.34–1.37)	0.287	0.52 (0.26–1.05)	0.067
LTI (H vs L)	0.23 (0.11–0.49)	0.000	0.30 (0.13–0.70)	0.005	**0.34 (0.15–0.78)**	**0.011**
CV events						
BMI (H vs L)	0.93 (0.58–1.50)	0.765	1.11 (0.69–1.79)	0.681	1.29 (0.78–2.13)	0.320
FTI (H vs L)	1.56 (0.96–2.54)	0.073	1.17 (0.70–1.98)	0.550	1.03 (0.60–1.77)	0.916
LTI (H vs L)	0.31 (0.18–0.53)	0.000	0.46 (0.25–0.86)	0.014	**0.53 (0.28–0.98)**	**0.042**

Lin TY, Hung SC et al. Kidney Int 93:733–740, 2018


CLINT EASTWOOD
THE GOOD
THE BAD
and THE UGLY
co-starring
LEE VAN CLEEF
also starring
ELI WALLACH
in the role of TUCO
directed by
SERGIO LEONE


THE BAD
THE GOOD
THE UGLY
OH
LTM
ATM

Misclassification of Obesity by BMI in CKD



Obesity diagnosis:

- BF% >25% in males and >35% in females
- BMI >28 according to the Working Group on Obesity in China

Lin TY, Hung SC et al. Kidney Int Rep 3:447–455, 2018

Misclassification of Obesity by BMI in CKD

Characteristics	Group I n = 63	Group II n = 28	Group III n = 139	**Group IV** n = 96	P
Body composition					
BMI (kg/m^2)	31.3 ± 3.3	29.7 ± 2.7	23.3 ± 2.4	24.9 ± 2.2	<0.001
BF (%)	34.3 ± 6.8	24.3 ± 5.9	20.4 ± 7.9	33.2 ± 6.0	<0.001
LTI (kg/m^2)	**15.7 ± 2.9**	**18.7 ± 2.6**	**16.1 ± 2.8**	**12.8 ± 2.4**	**<0.001**
Demographics					
Age (yr)	63.1 ± 13.7	56.7 ± 13.1	64.2 ± 12.5	72.5 ± 11.4	<0.001
Male sex, n (%)	49 (77.8)	17 (60.7)	93 (66.9)	65 (67.7)	0.321
DM, n (%)	43 (68.3)	15 (53.6)	46 (33.1)	44 (45.8)	<0.001
CVD, n (%)	18 (28.6)	5 (17.9)	27 (19.4)	27 (28.1)	0.283
Clinical parameters					
eGFR (ml/min per 1.73 m^2)	32.5 ± 15.6	32.1 ± 12.8	28.2 ± 15.3	26.3 ± 13.2	0.039
UPCR (g/g)	0.82 (0.33–2.45)	2.27 (0.29–5.17)	0.91 (0.32–2.25)	0.84 (0.30–1.81)	0.404
Albumin (g/dl)	3.6 ± 0.4	3.5 ± 0.5	3.6 ± 0.5	3.6 ± 0.4	0.641
hs-CRP (mg/l)	5.4 (2.2–12.6)	3.9 (1.9–8.9)	3.0 (1.0–8.9)	4.5 (1.7–10.6)	0.034

Lin TY, Hung SC et al. Kidney Int Rep 3:447–455, 2018

Misclassification of Obesity and Mortality in CKD

Patient group	Unadjusted		Model 1		Model 2	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Group I	1		1		1	
Group II	0.89 (0.09, 8.53)	0.917	1.04 (0.11, 10.19)	0.975	0.80 (0.08, 8.06)	0.852
Group III	2.19 (0.62, 7.69)	0.223	2.15 (0.61, 7.58)	0.234	2.65 (0.72, 9.75)	0.143
Group IV	**6.06 (1.81, 20.30)**	**0.003**	**4.61 (1.36, 15.71)**	**0.014**	**5.17 (1.44, 18.60)**	**0.012**

Lin TY, Hung SC et al. Kidney Int Rep 3:447–455, 2018

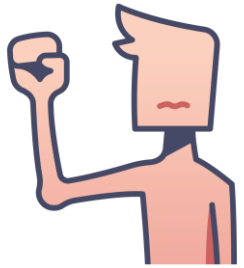
Limitations of BMI-based Definition of Obesity

BMI-based definition of obesity

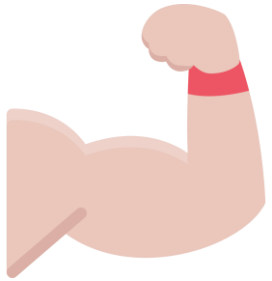
BF% >25% in males
or >35% in females

Normal BMI
No excess fat mass

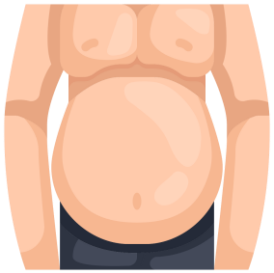
Normal BMI
Excess fat mass



Obesity
No excess fat mass

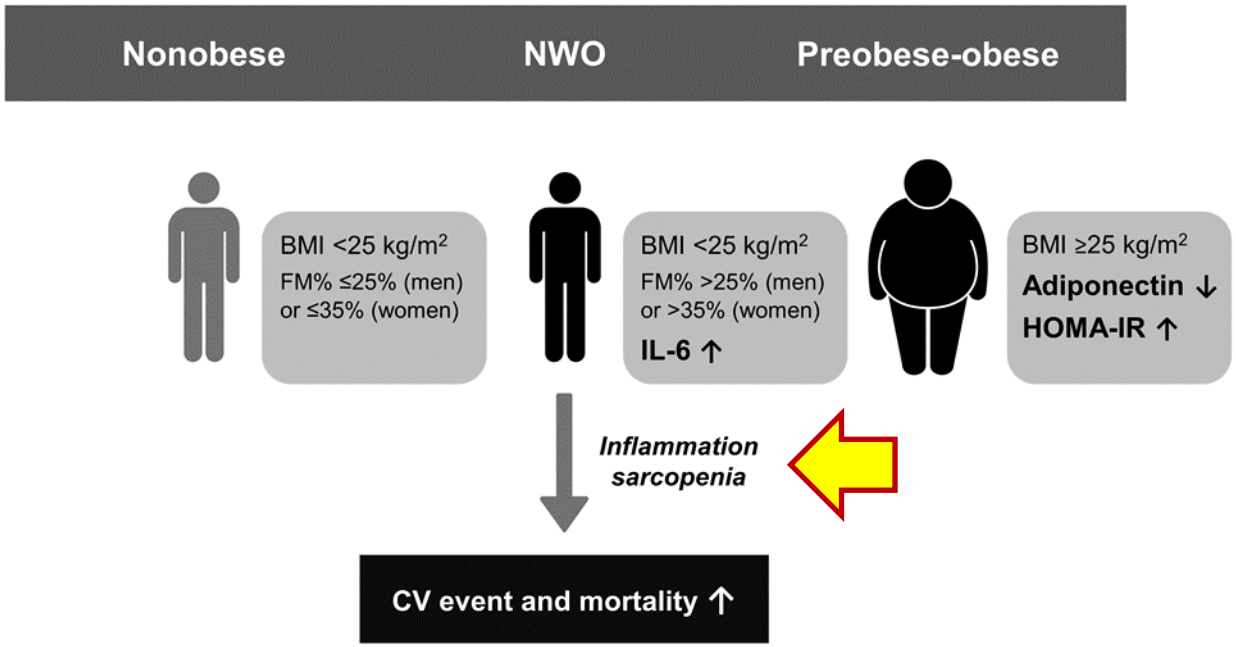


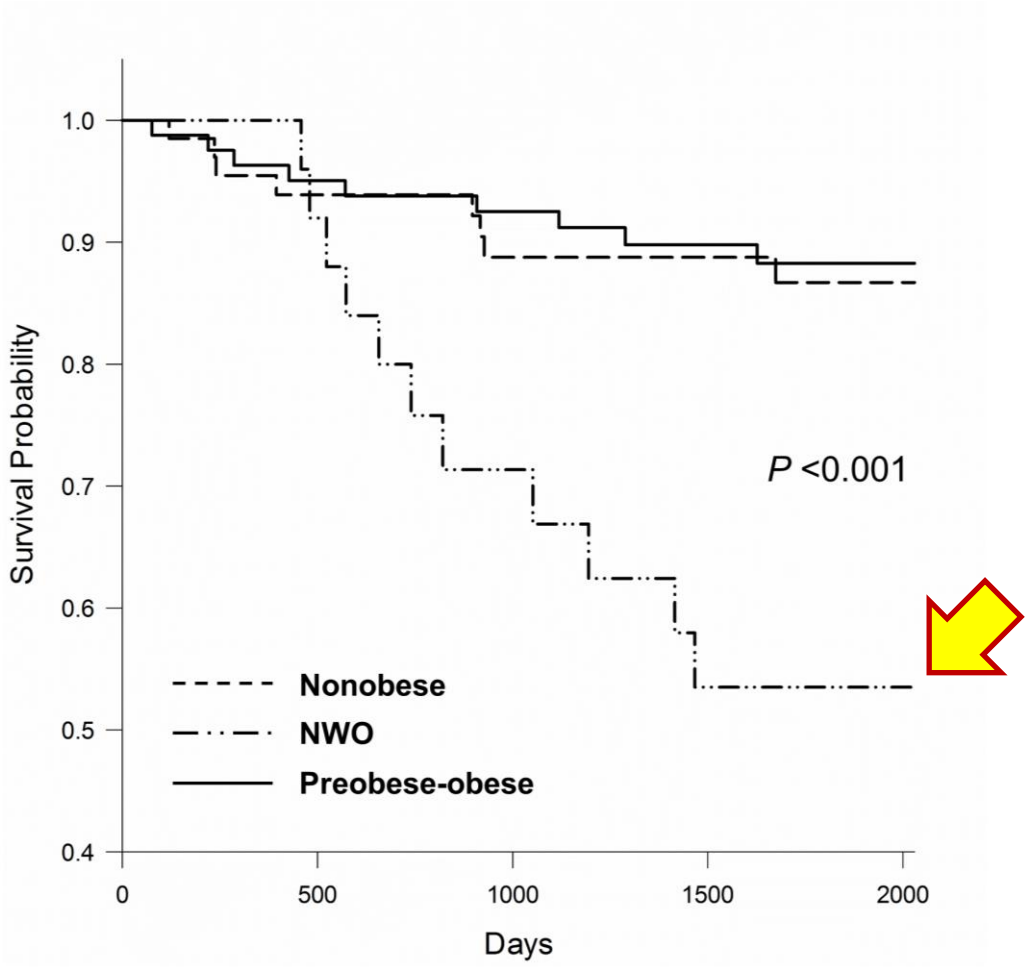
Obesity
Excess fat mass



Normal weight obesity

Normal Weight Obesity and Outcomes in CKD

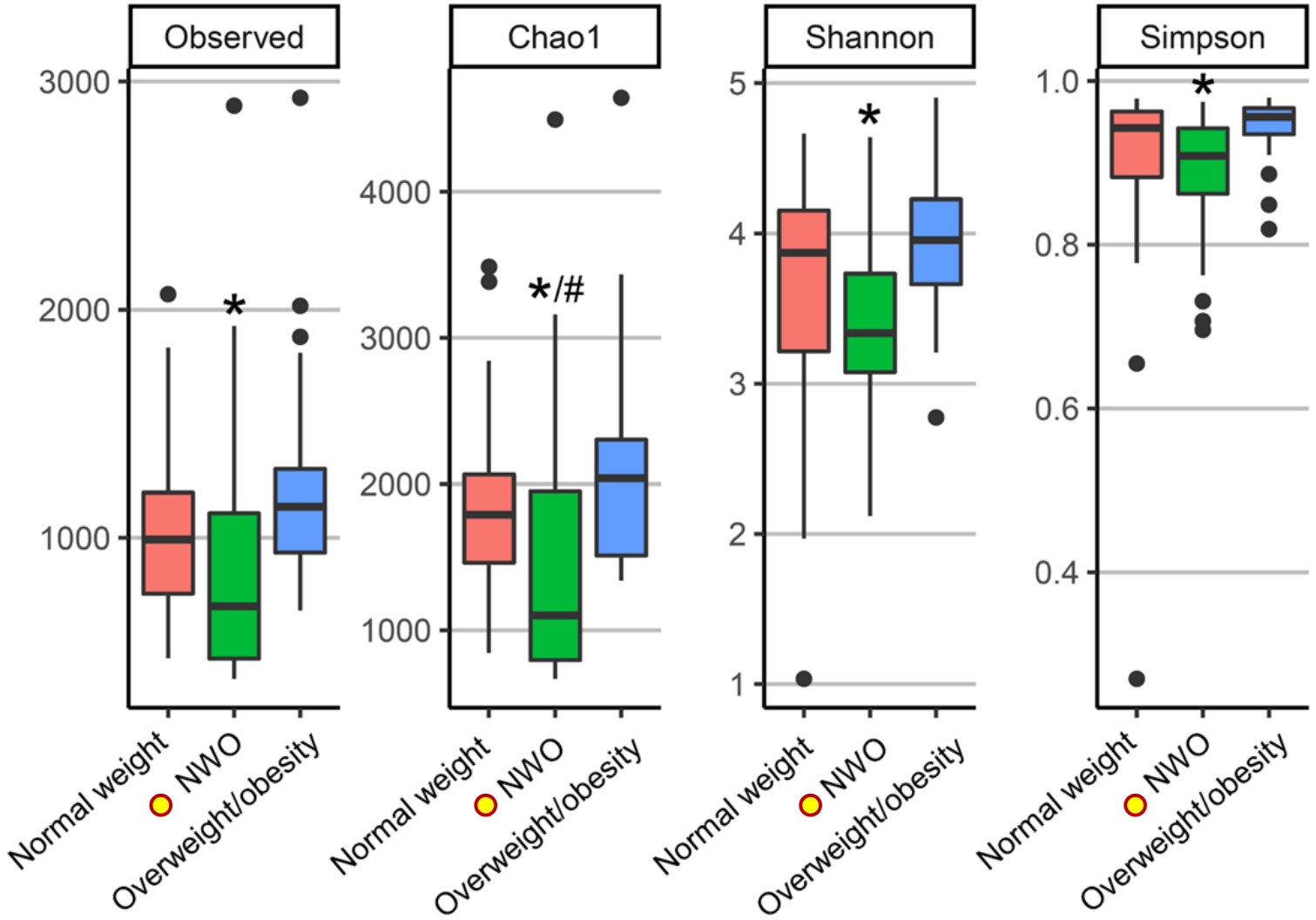




Lin TY, Hung SC et al. Am J Clin Nutr 107:664–672, 2018

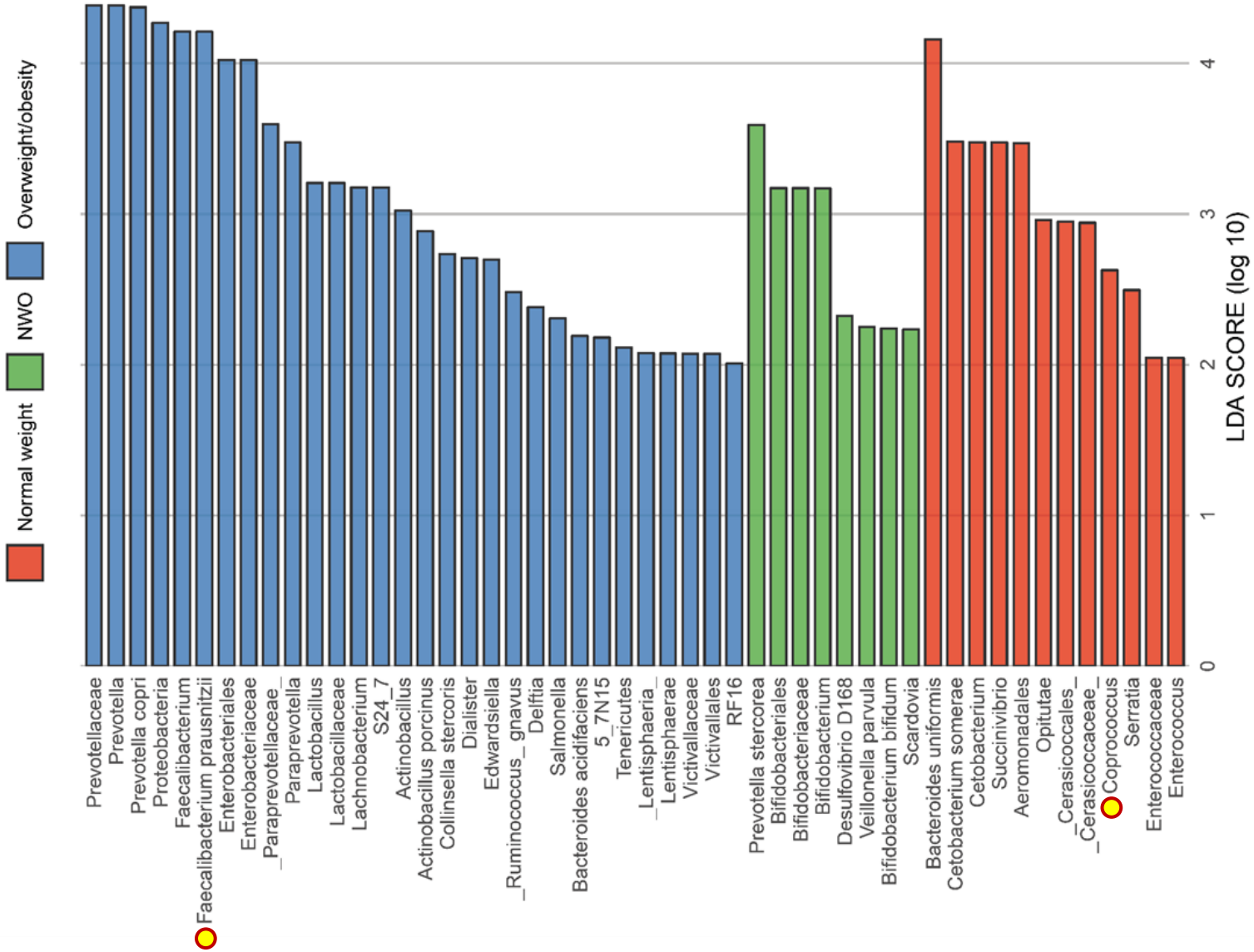
Gut Microbiota and Body Composition in HD Patients

OUT-level, $^{*}P$ = 0.001 vs. overweight/obesity; $^{\#}P$ <0.05 vs. normal weight



Lin TY, Hung SC et al. J Clin Endocrinol Metab 105:2006–2014, 2020

Gut Microbiota and Body Composition in HD Patients



Lin TY, Hung SC et al. J Clin Endocrinol Metab 105:2006–2014, 2020

Nutritional Supplement in HD Patients with NWO

Trial profile

Patients assessed for eligibility (n=512)

Not meeting inclusion criteria (n=458)
Refused to participate (n=3)
Other reasons (n=0)

Patients randomized to treatment (n=51)

Nutritional counselling (n=25)

Nutritional supplements (n=26)

One can (237 ml) daily

calories 425 kcal, 19.1 g protein,

22.7 g fat, 37.9 g carbohydrate

Ineligible (n=1)
Voluntary withdrawal (n=1)
Deceased (n=2)

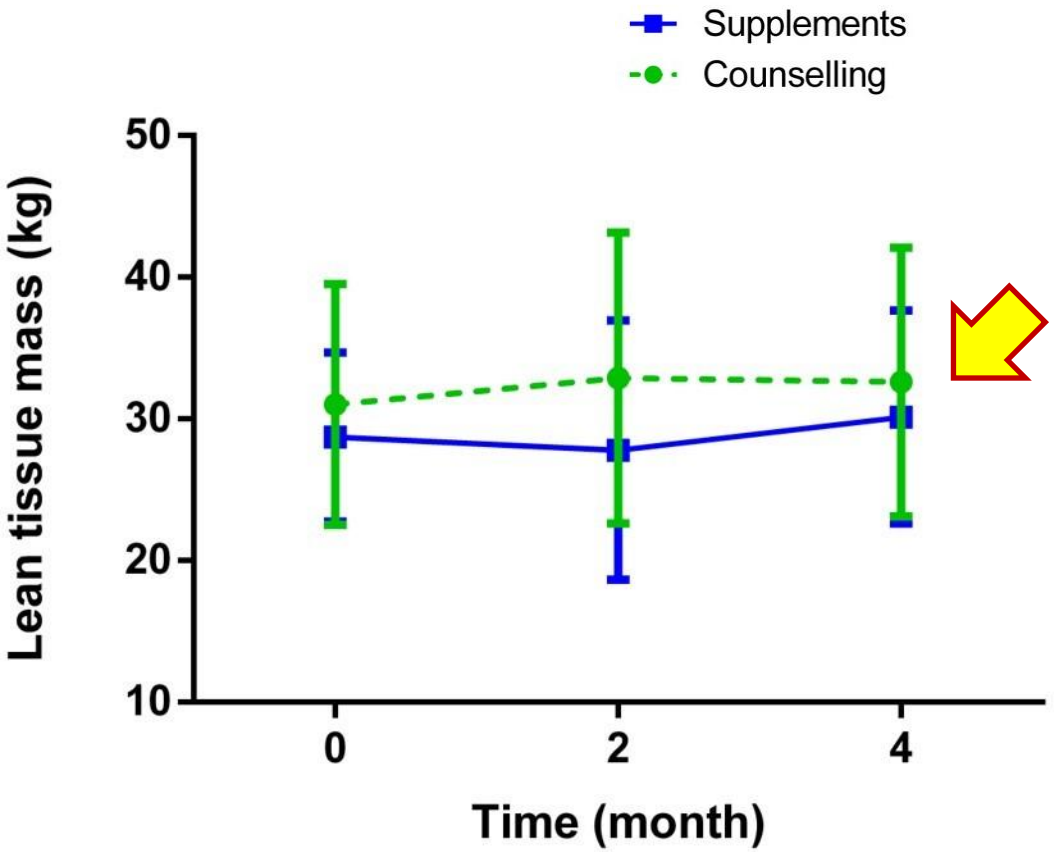
Ineligible (n=1)
Discontinued supplements (n=3)
Deceased (n=1)

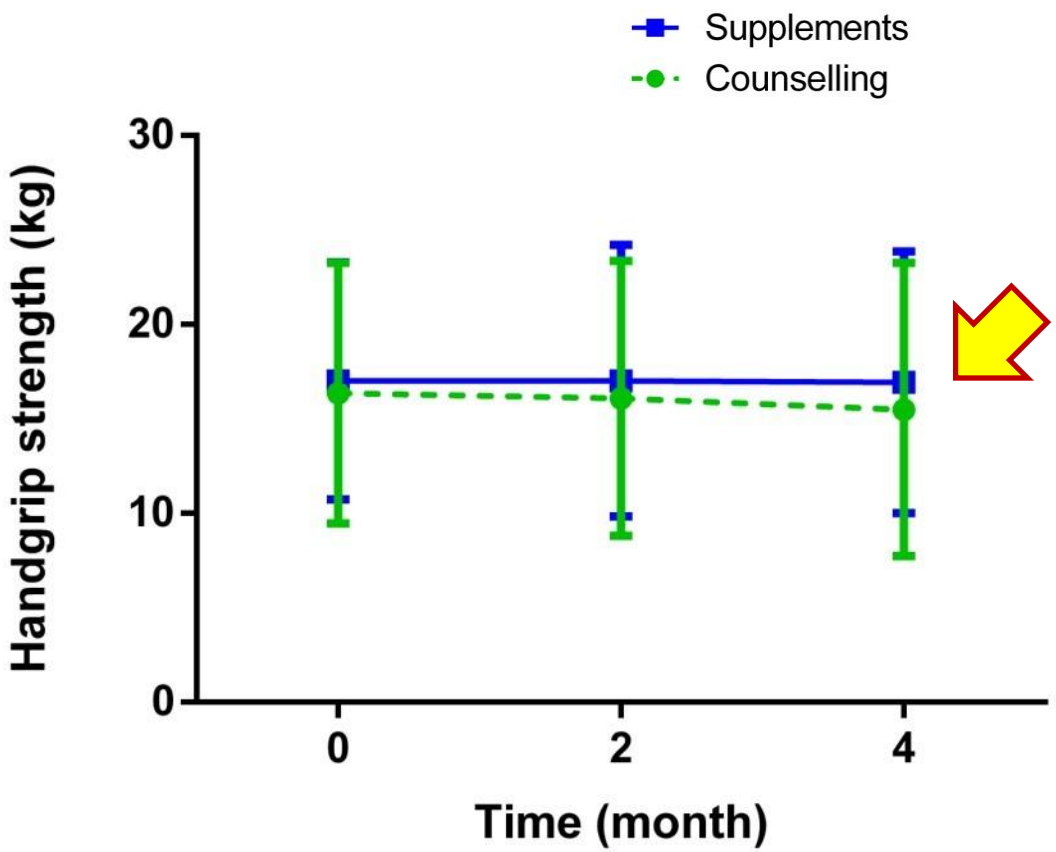
Full analysis set (n=24)
Per protocol set (n=21)

Full analysis set (n=25)
Per protocol set (n=21)

Lin TY, Hung SC et al. Nephrol Dial Transplant 34 (Suppl 1):gfz103.SP382, 2019

Nutritional Supplement in HD Patients with NWO





Lin TY, Hung SC et al. Nephrol Dial Transplant 34 (Suppl 1):gfz103.SP382, 2019

Two Types of Malnutrition in CKD

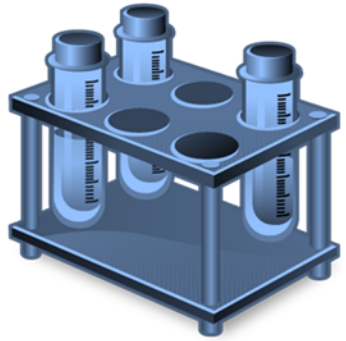
Type-1	Mixed type	Type-2
	Inflammation 	
Non-inflammatory components		
Co-morbidity: None	May be present	Common and severe

Peter Stenvinkel

Stenvinkel P et al. Nephrol Dial Transplant 15:953–960, 2000

ISRNM Criteria of PEW

A state of decreased body stores of protein and energy fuels
diagnosed by 1 positive result in at least 3 of the following 4 categories

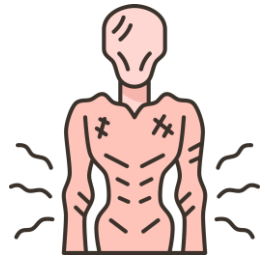


- Alb <3.8 g/dL (BCG)
- Prealbumin <30 mg/dL
- Cholesterol <100 mg/dL

SERUM CHEMISTRY

- Muscle loss 5% in 3 mos
- Reduced MAMC >10%
- Creatinine appearance

MUSCLE MASS



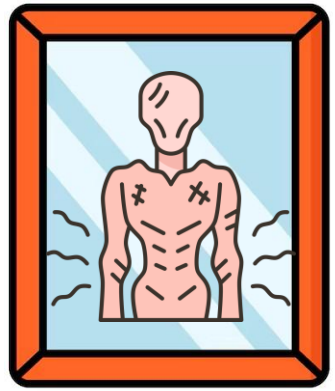
Cachexia

- BMI <23 g/dL
- Weight loss 5% in 3 mos
- Total BF% <10%

BODY MASS

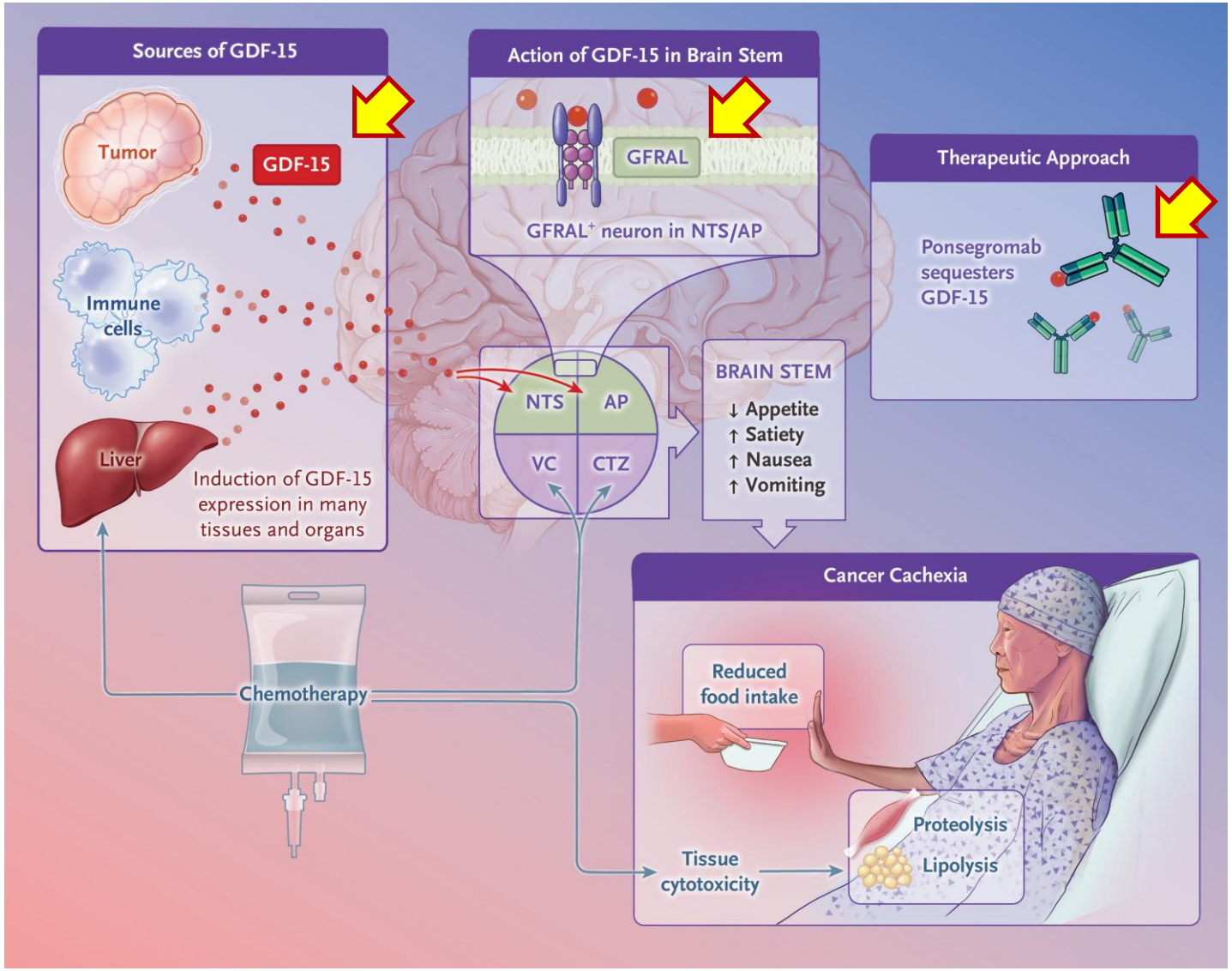
- DPI <0.8 g/kg/day
- DEI <25 kcal/kg/day

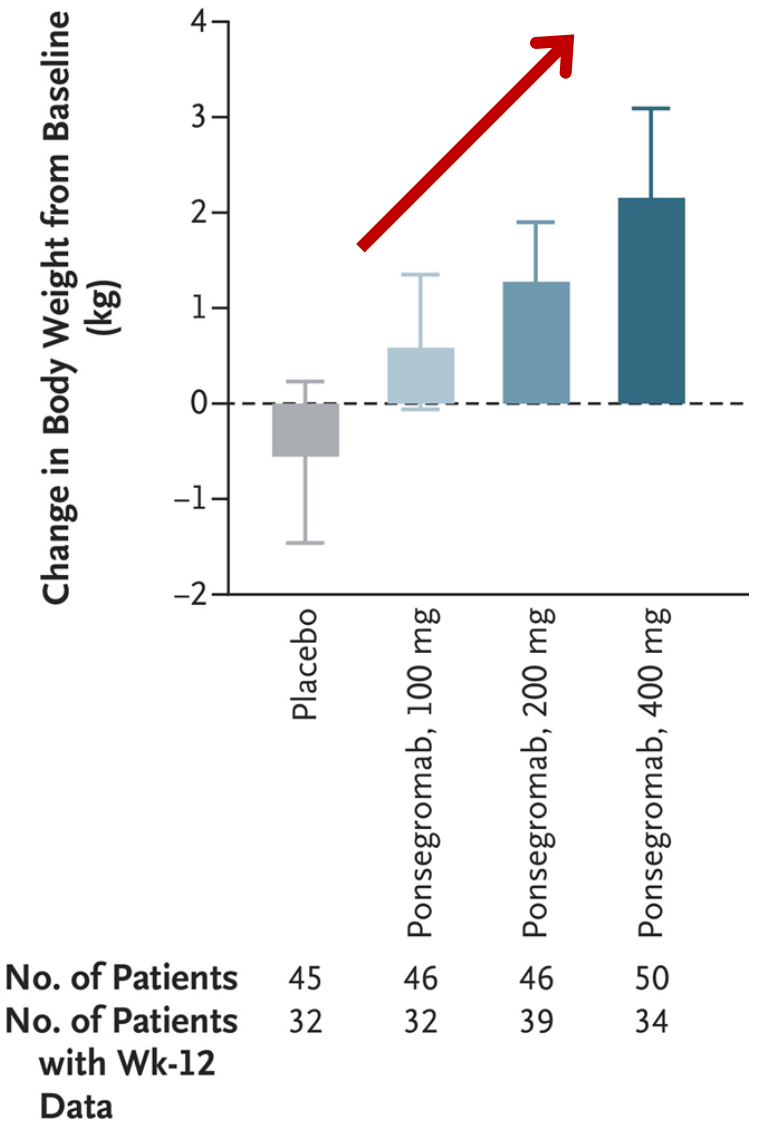
DIETARY INTAKE



NWO

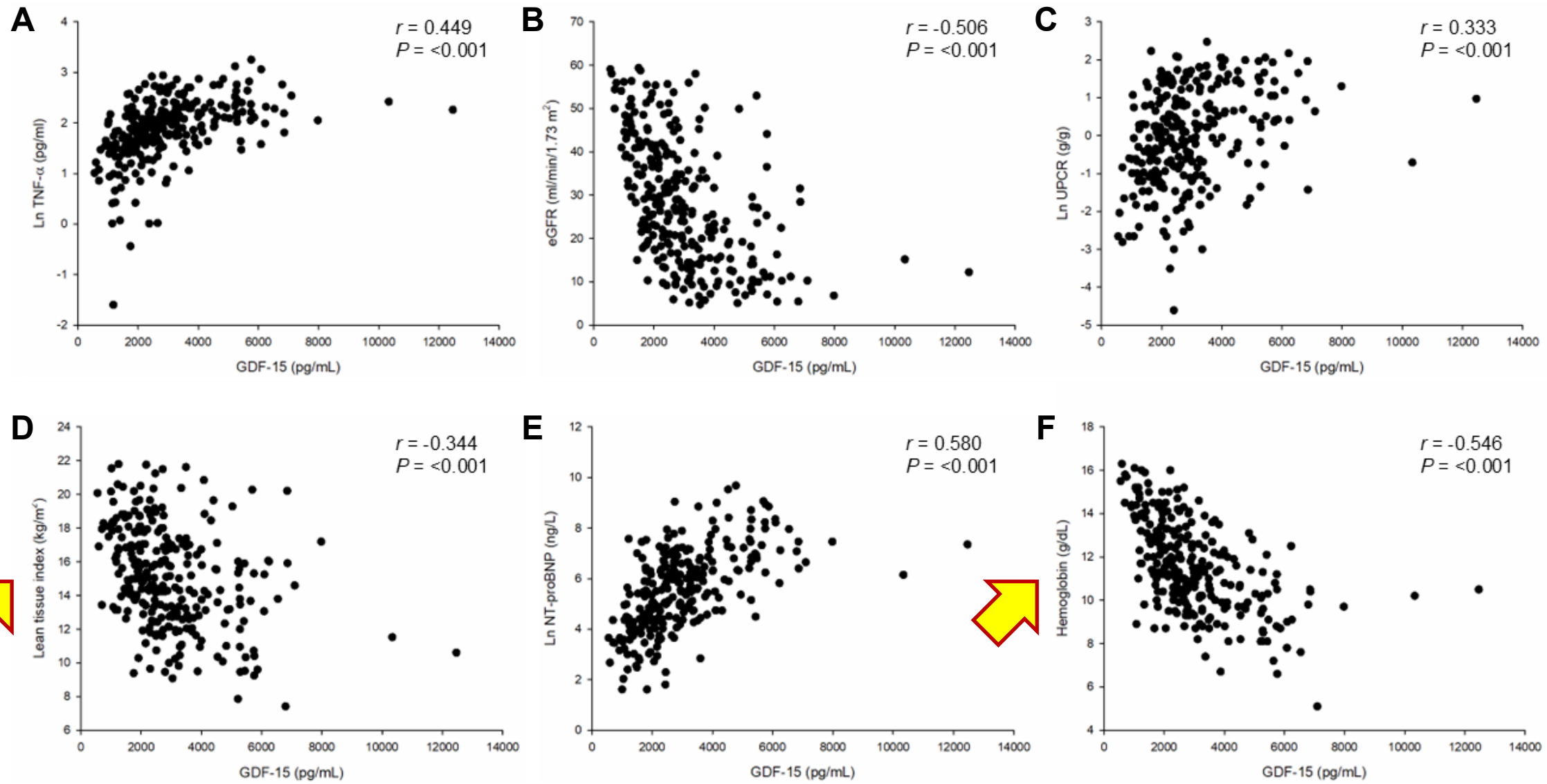
Ponsegromab in Cancer Cachexia





Baracos VE. NEJM 391:2373–2376, 2024; Groarke JD et al. NEJM 391:2291–2303, 2024

GDF-15 and Cachexia in CKD

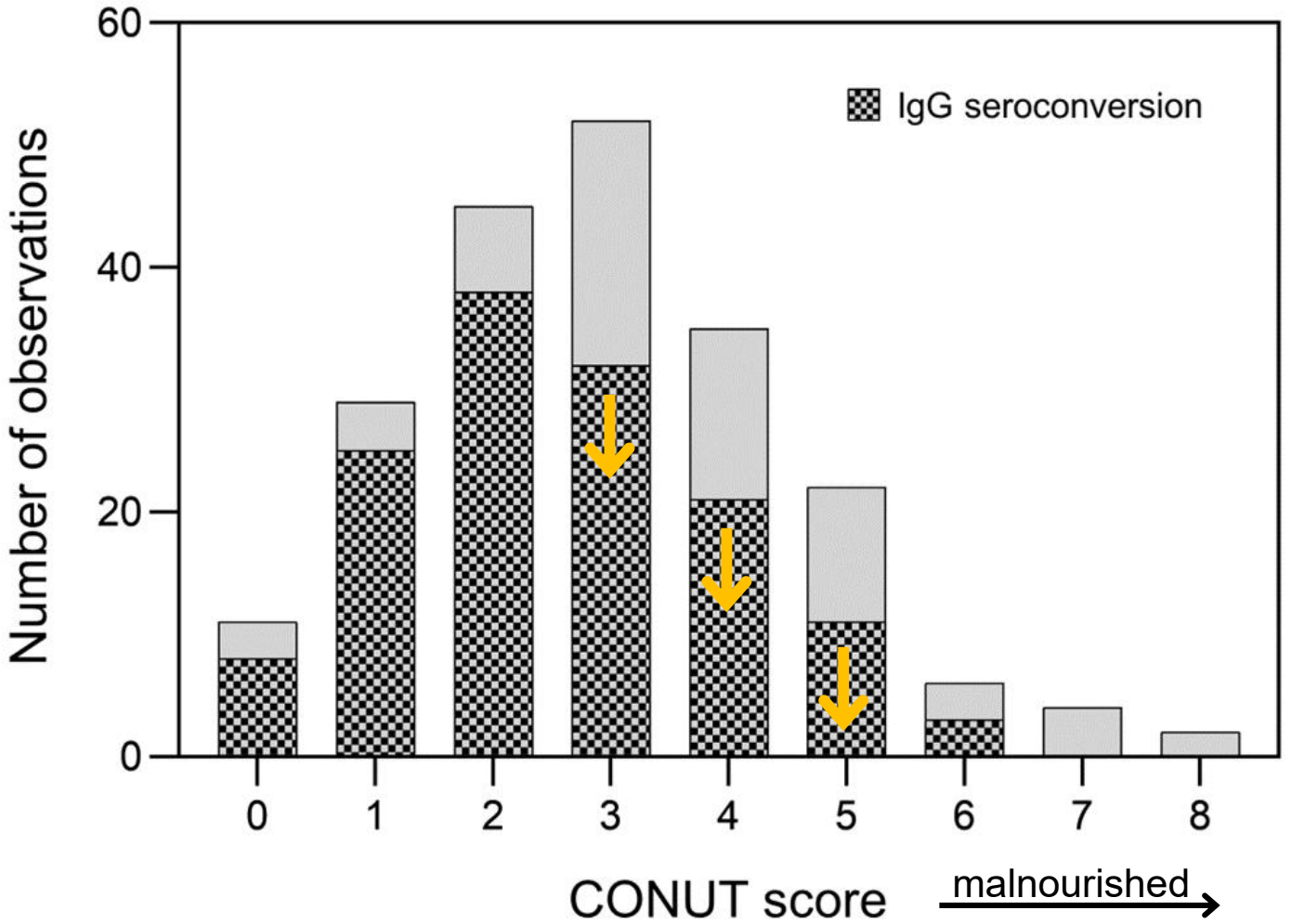


Hung SC 2025

Summary 1

- A higher BMI is paradoxically linked to lower mortality in CKD, reflecting the benefit of greater lean body mass over fat.
- Many CKD patients exhibit excess body fat with normal BMI, leading to misclassification of obesity by BMI.
- NWO in CKD is characterized by inflammation and sarcopenia. Nutritional supplement does not improve nutritional status in CKD patients with NWO.
- GDF-15 is associated with muscle wasting and anemia in CKD. Therapeutic modulation of GDF-15 shows promise in cancer cachexia and may translate to CKD-related cachexia.

Malnutrition and SARS-CoV-2 Vaccine Response in HD



Lin TY, Hung SC et al. Clin Nutr 41:2683–2690, 2022

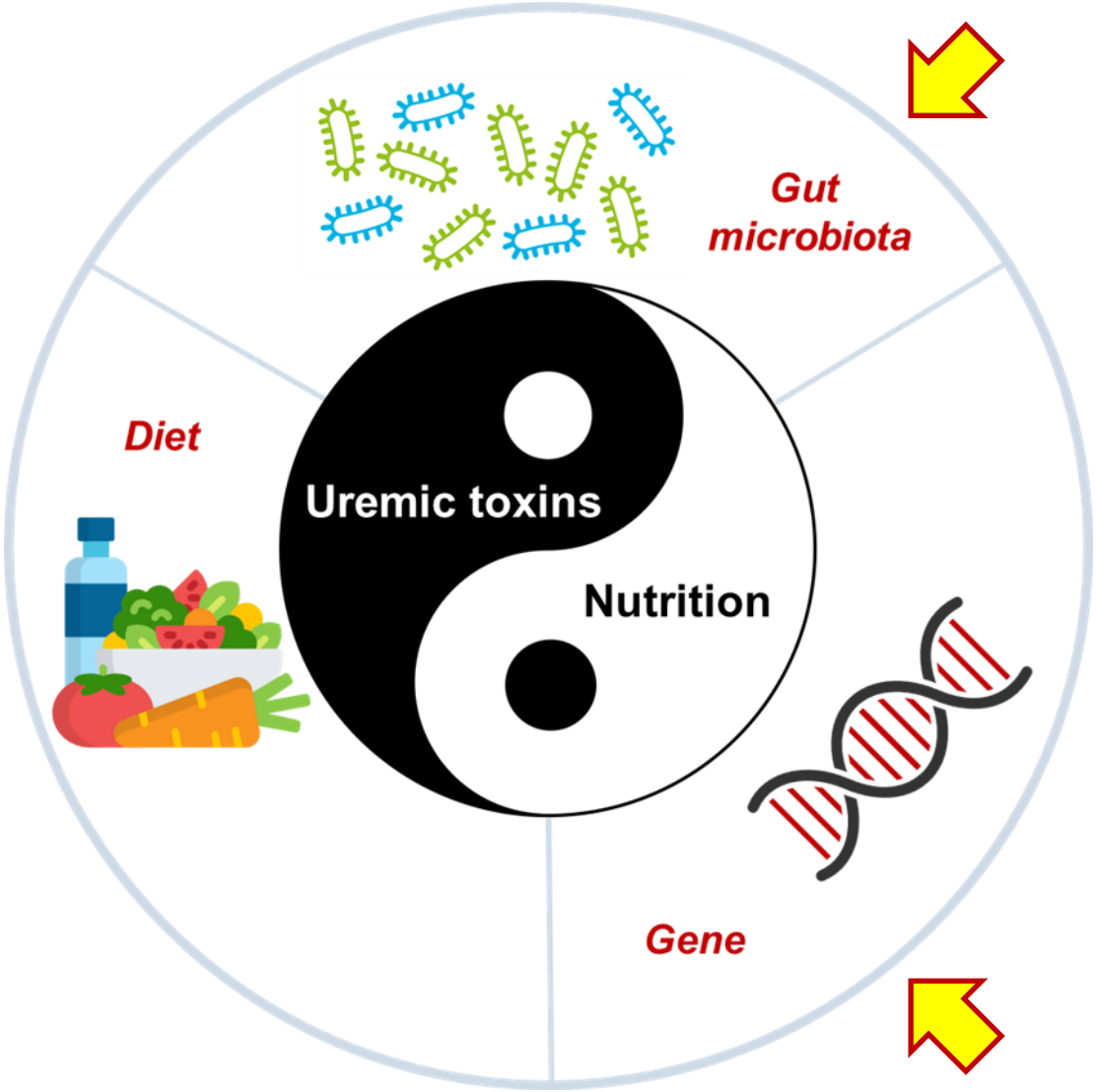
nutrition

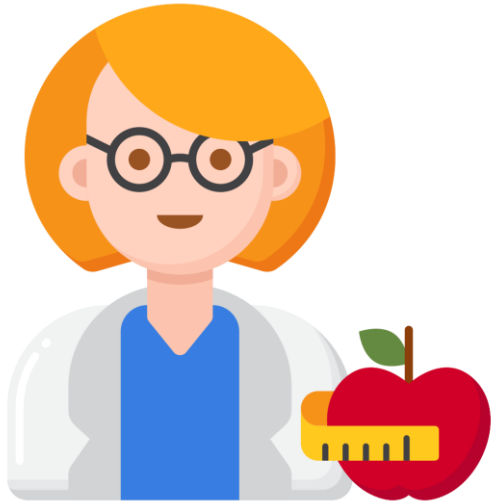
“the substances that you take into your body as food and the way that they influence your health”

Cambridge Dictionary

Ying and Yang of Nutritional Therapy in CKD

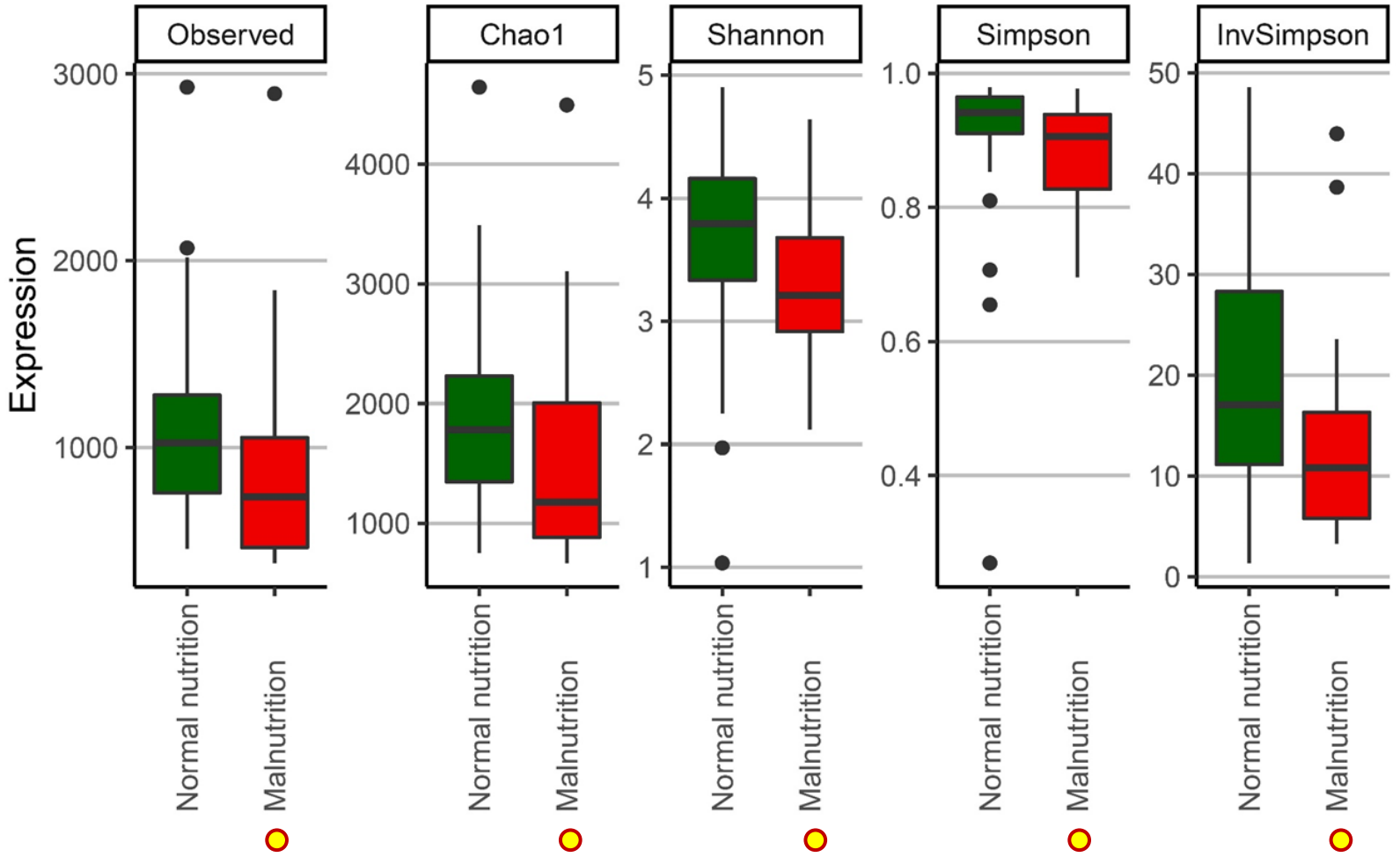
Nephrocentric view





Nutricentric view

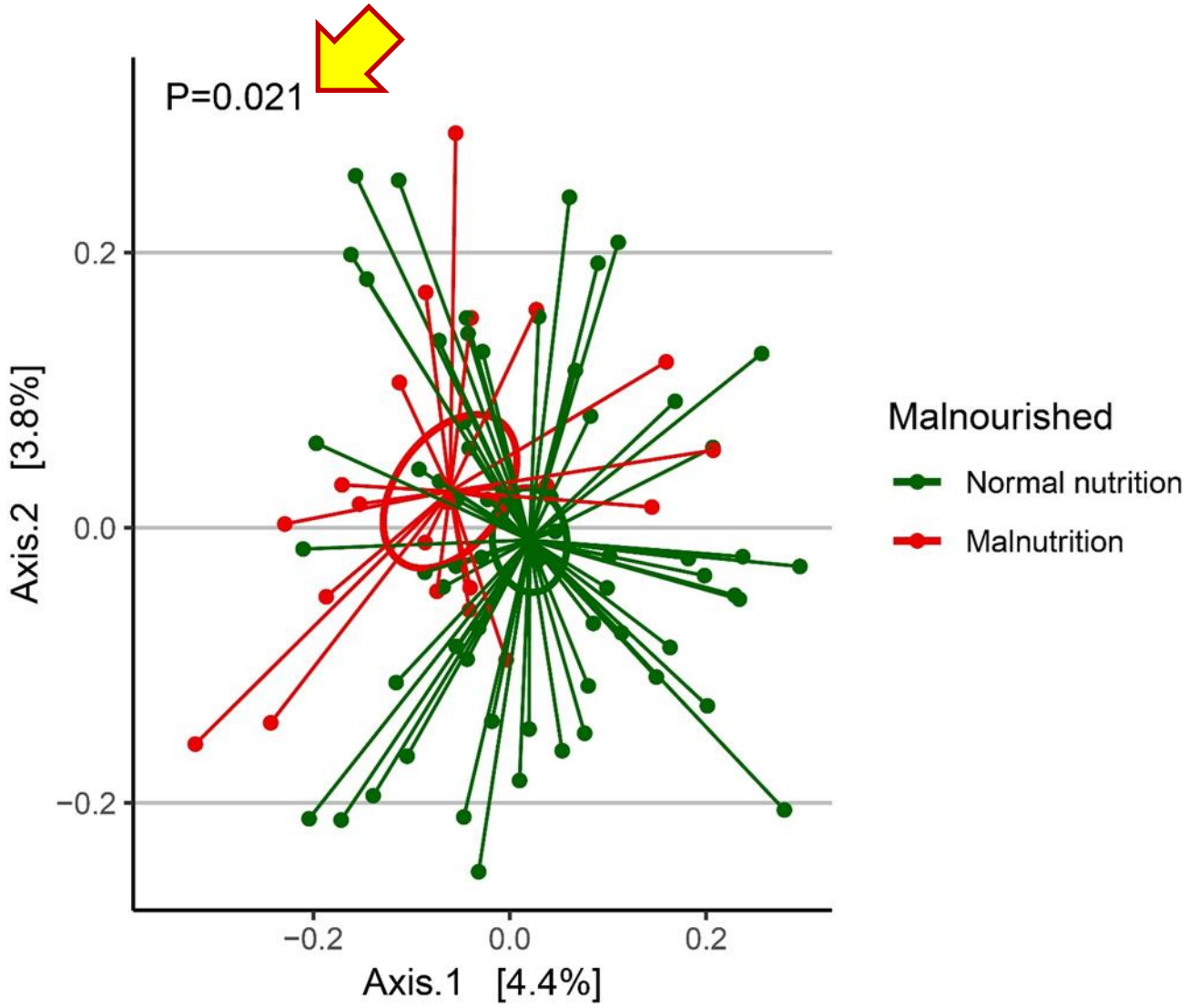
Gut Dysbiosis and Malnutrition in HD Patients



Malnutrition (SGA scores 1–5), Normal nutrition (SGA scores 6–7); 16S rRNA gene sequencing; OTU-level, all P <0.05

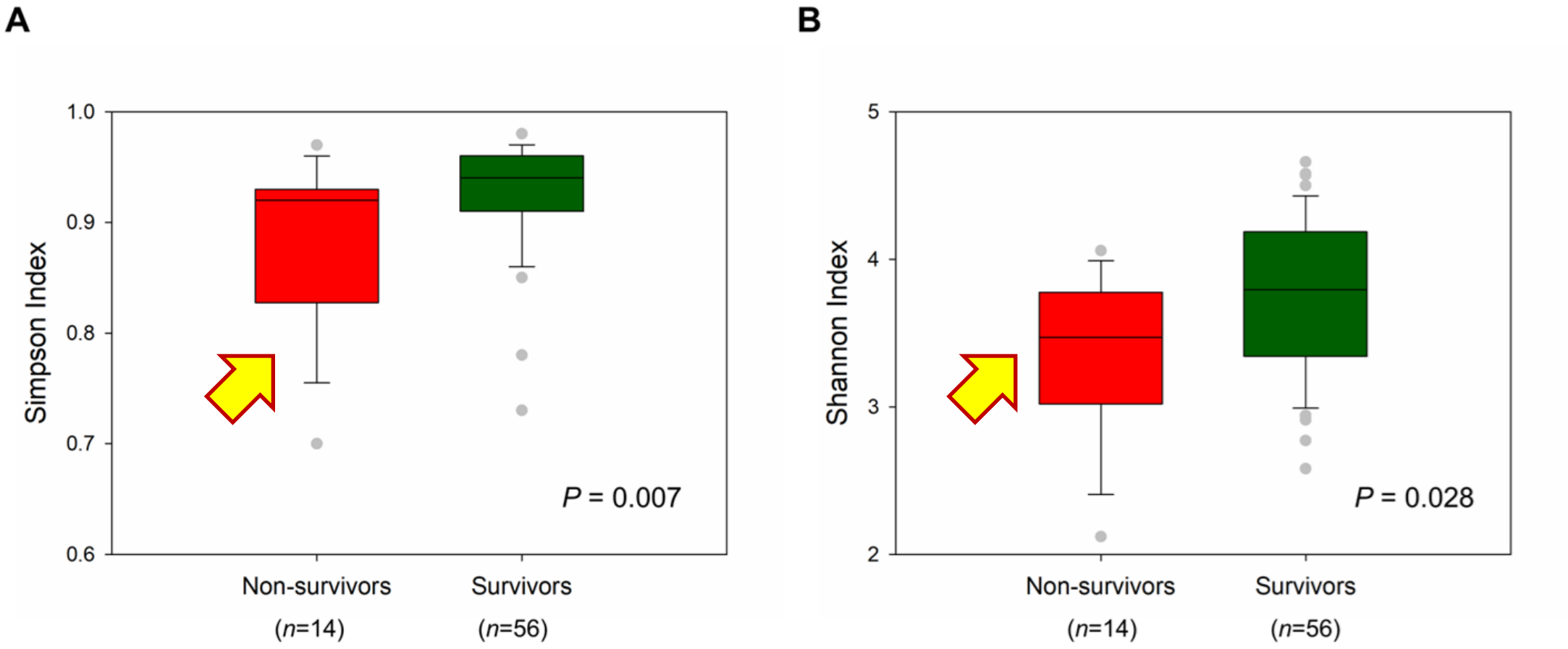
Lin TY, Hung SC et al. Nephrol Dial Transplant 36:1104–1111, 2021

Gut Dysbiosis and Malnutrition in HD Patients



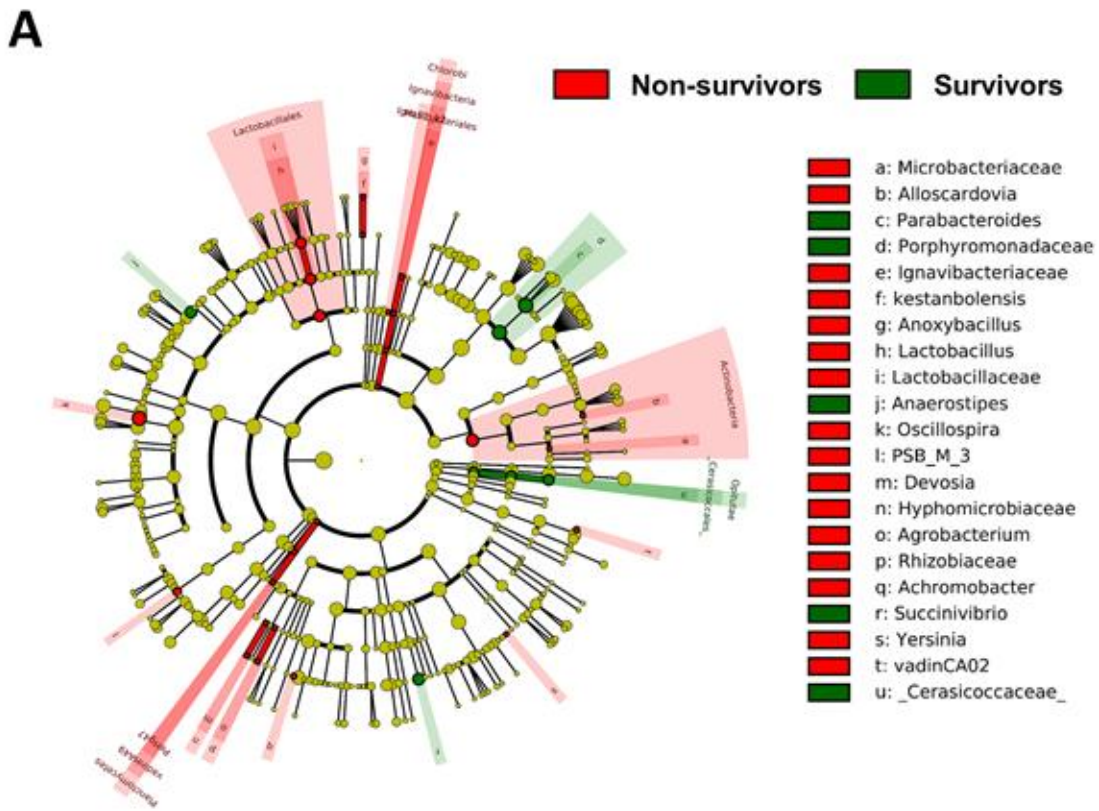
Lin TY, Hung SC et al. Nephrol Dial Transplant 36:1104–1111, 2021

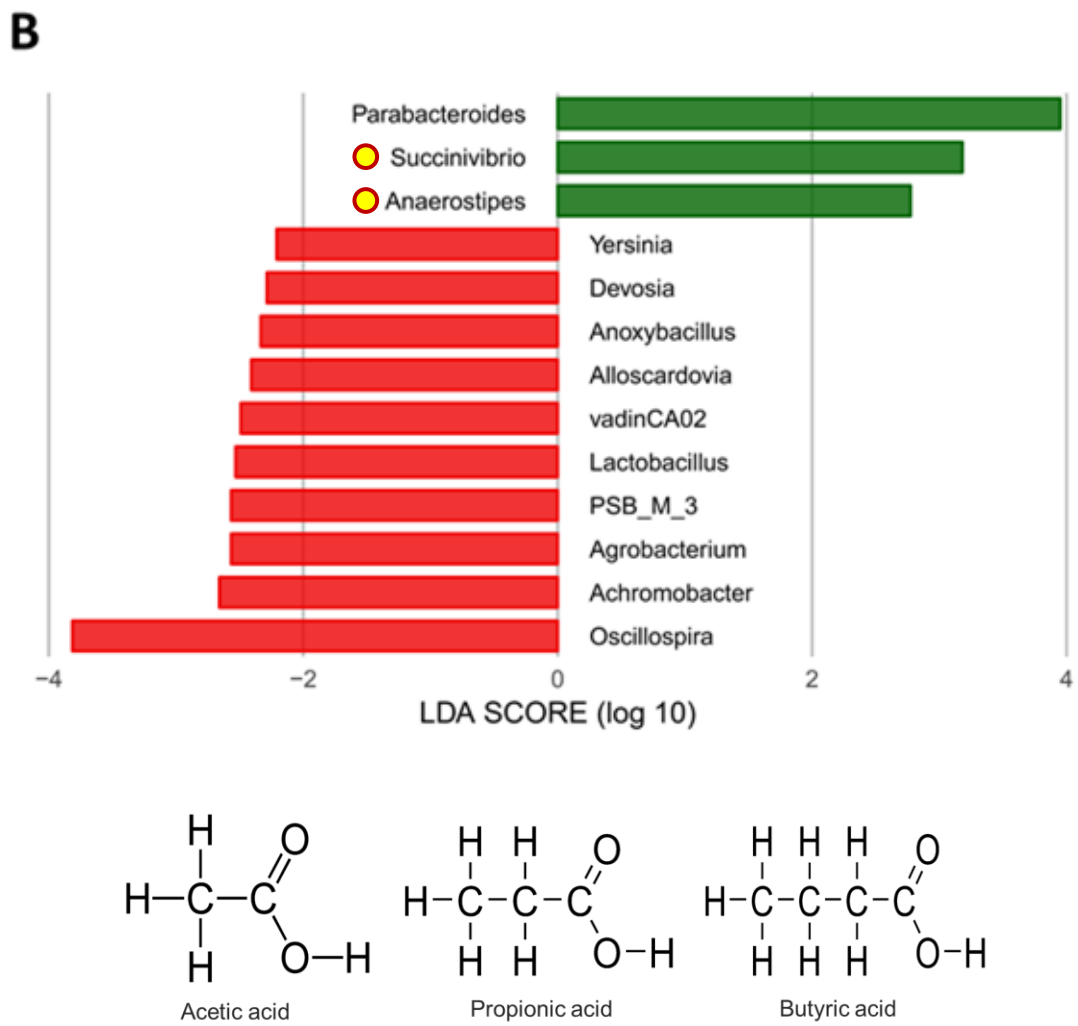
Gut Dysbiosis and Mortality in HD Patients



Lin YT, Hung SC et al. NPJ Biofilms Microbiomes 7:20, 2021

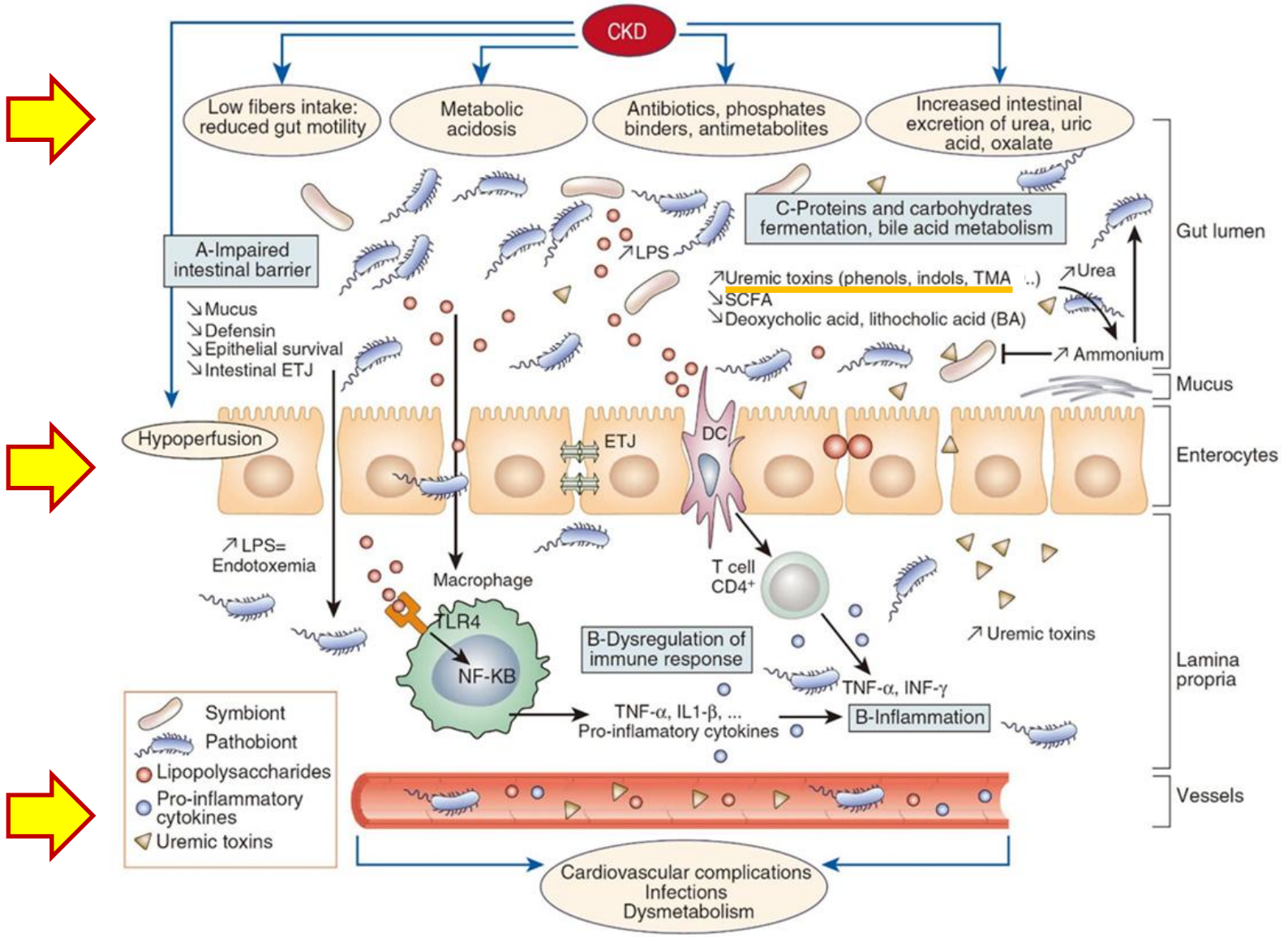
Gut Dysbiosis and Mortality in HD Patients





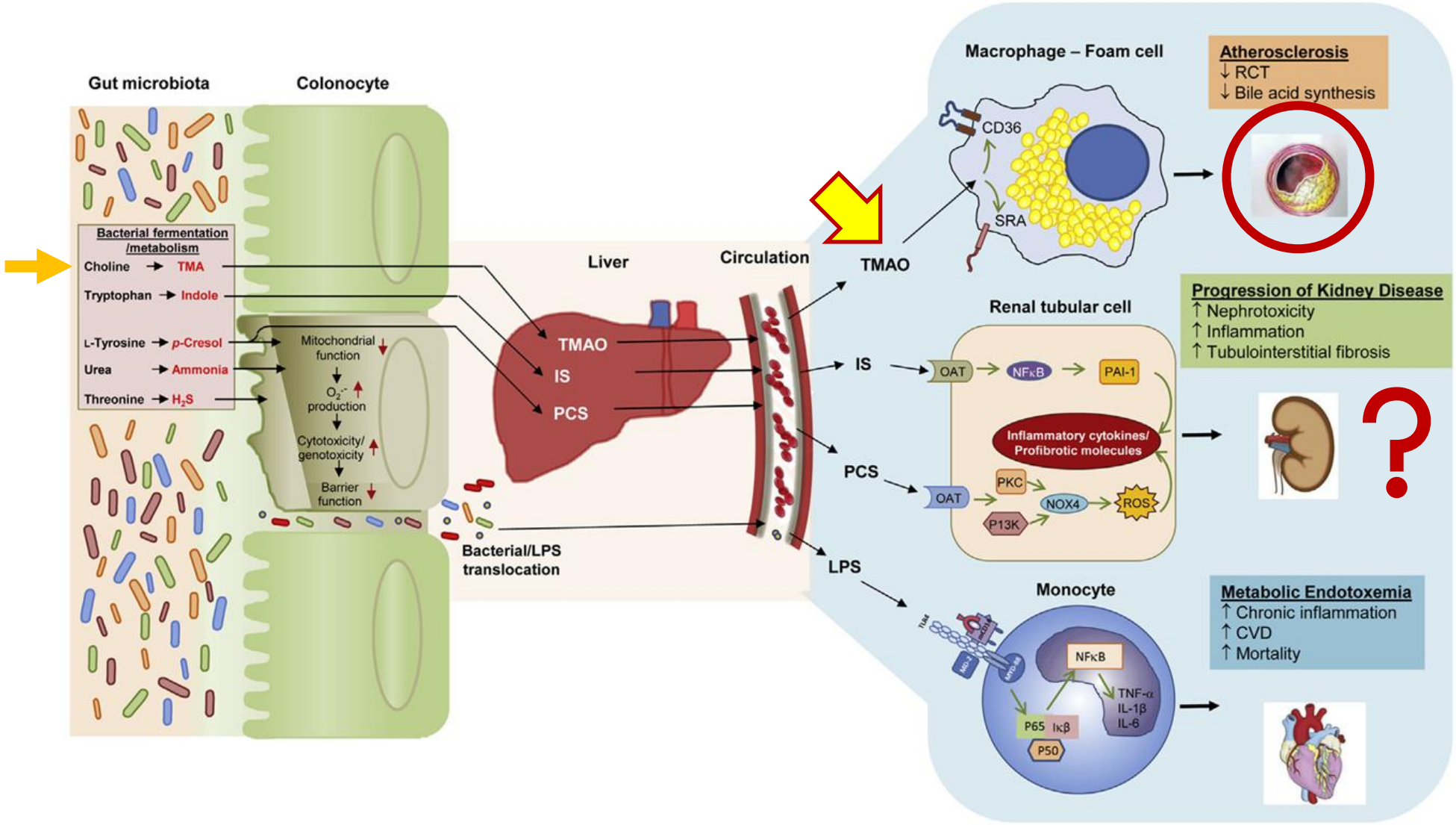
Lin TY, Hung SC et al. NPJ Biofilms Microbiomes 7:20, 2021

Gut Dysbiosis in CKD



Koppe L et al. Kidney Int 88:958–966, 2015

Gut-Derived Uremic Toxin: TMAO



Ramezani A et al. Am J Kidney Dis 67:483–498, 2016

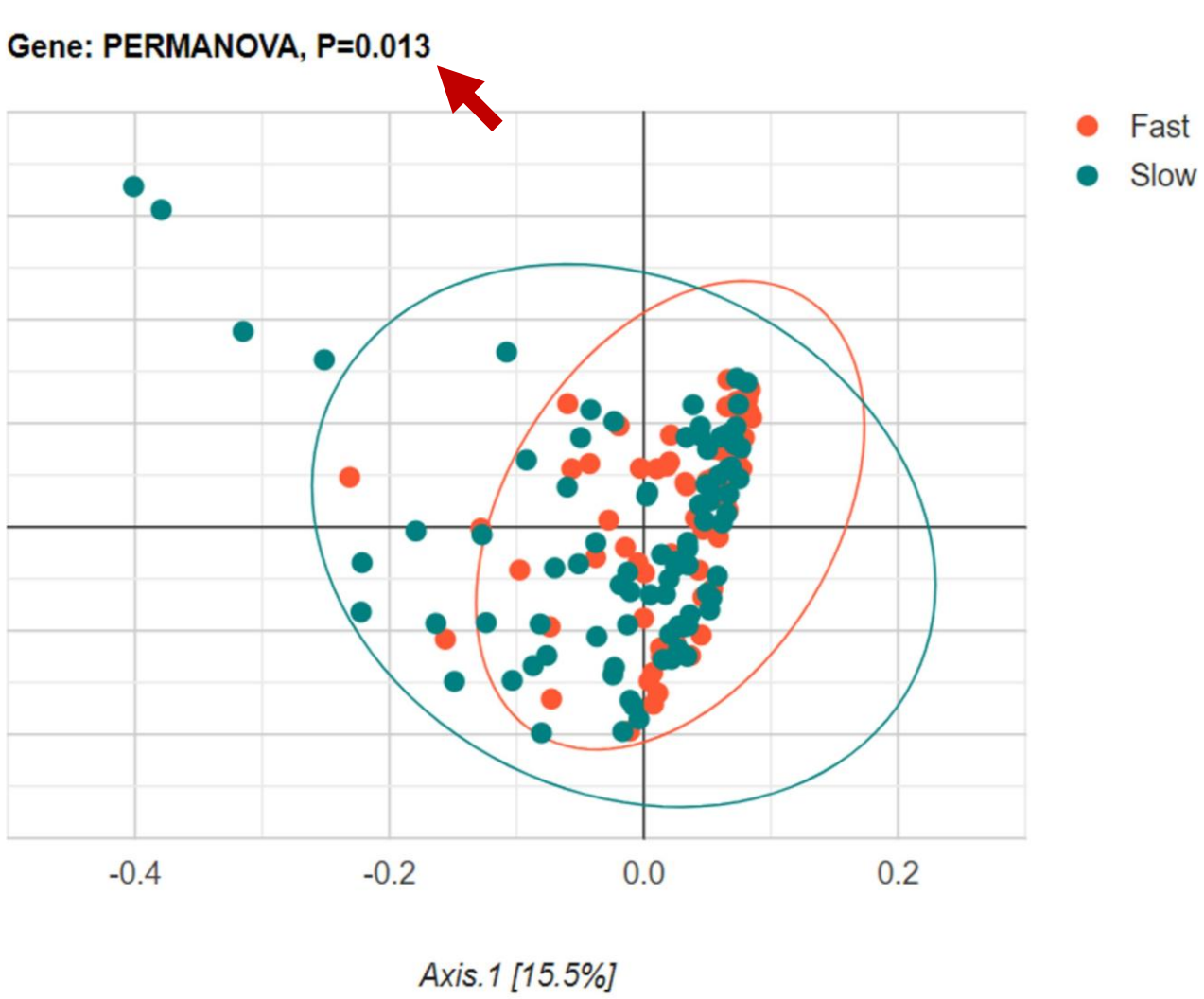
TMAO and Faster eGFR Decline in CKD

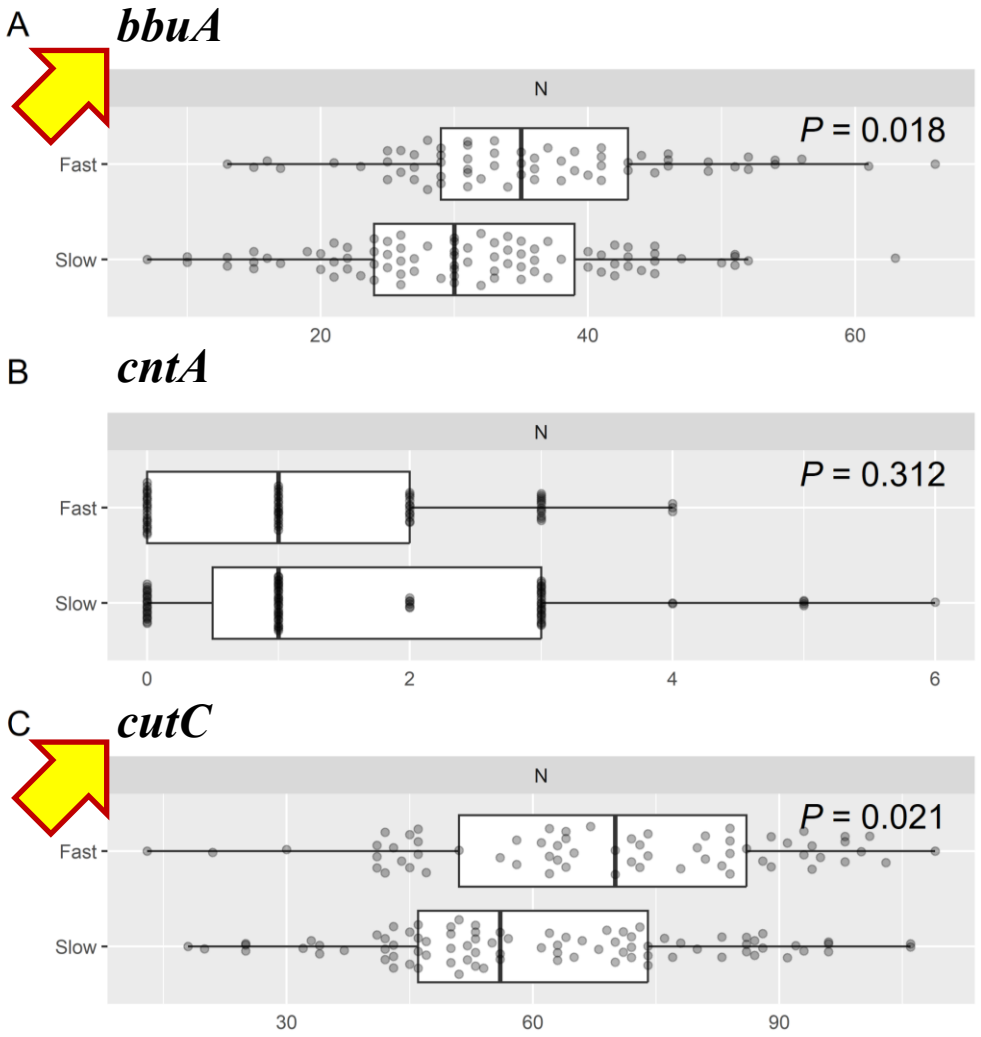
	Crude		Model 1		Model 2	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
TMAO, μM	**1.43 (1.02–2.00)**	**0.039**	**1.54 (1.09–2.19)**	**0.016**	**2.42 (1.36–4.32)**	**0.003**
TMA, μM	1.26 (0.91–1.76)	0.167	1.32 (0.94–1.86)	0.109	1.34 (0.84–2.14)	0.226
Choline, μM	0.93 (0.67–1.28)	0.648	0.92 (0.66–1.28)	0.628	0.94 (0.63–1.41)	0.776
Carnitine, μM	0.75 (0.54–1.04)	0.088	0.76 (0.55–1.06)	0.106	0.73 (0.49–1.09)	0.124
γ-Butyrobetaine, μM	0.92 (0.67–1.28)	0.628	0.90 (0.63–1.27)	0.541	1.09 (0.66–1.81)	0.741

(Fast eGFR decline is defined as a decrease in eGFR of >3 ml/min/1.73 m^2/year)

Hung SC et al. Clin Nutr 44:239–247, 2025

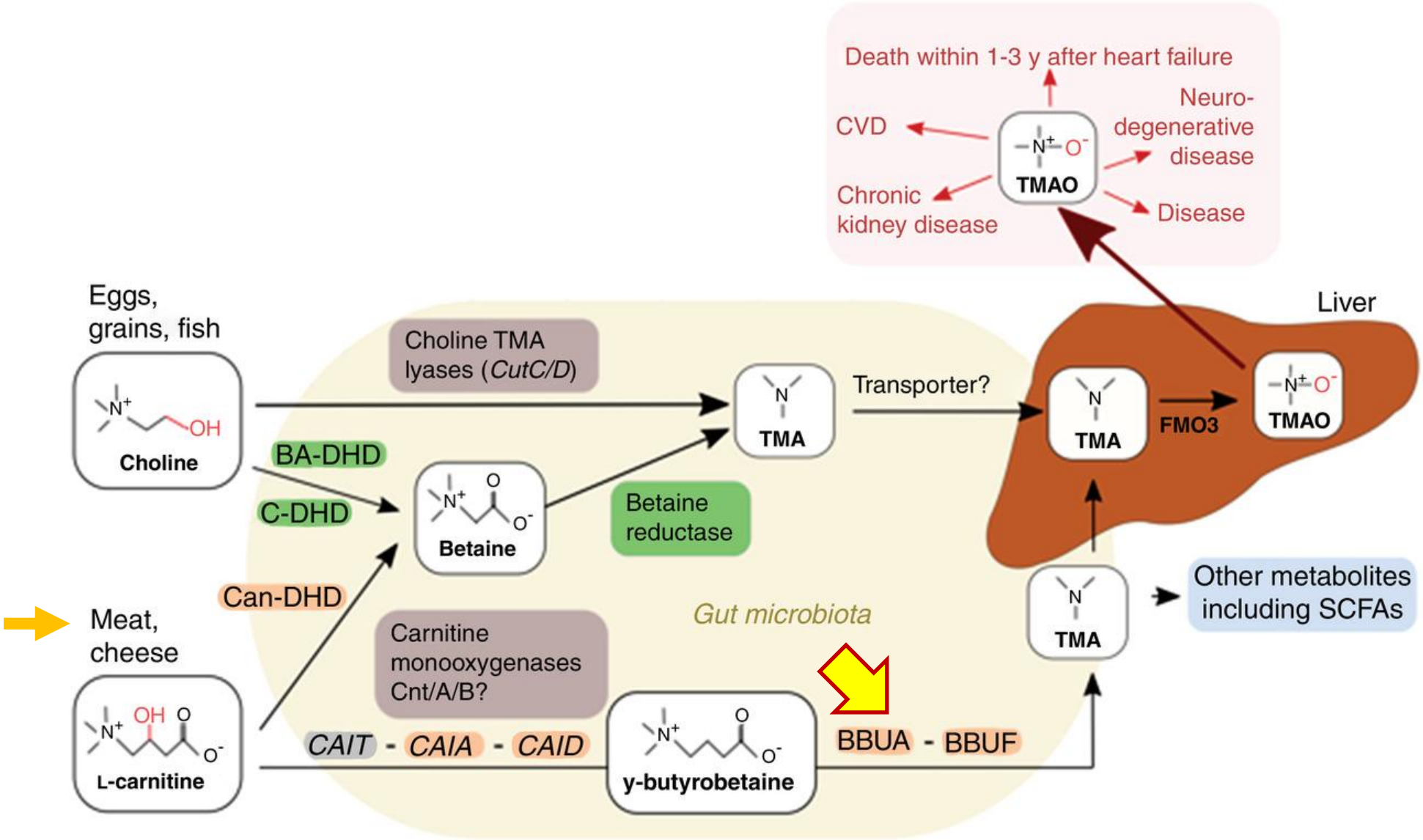
TMAO and Faster eGFR Decline in CKD





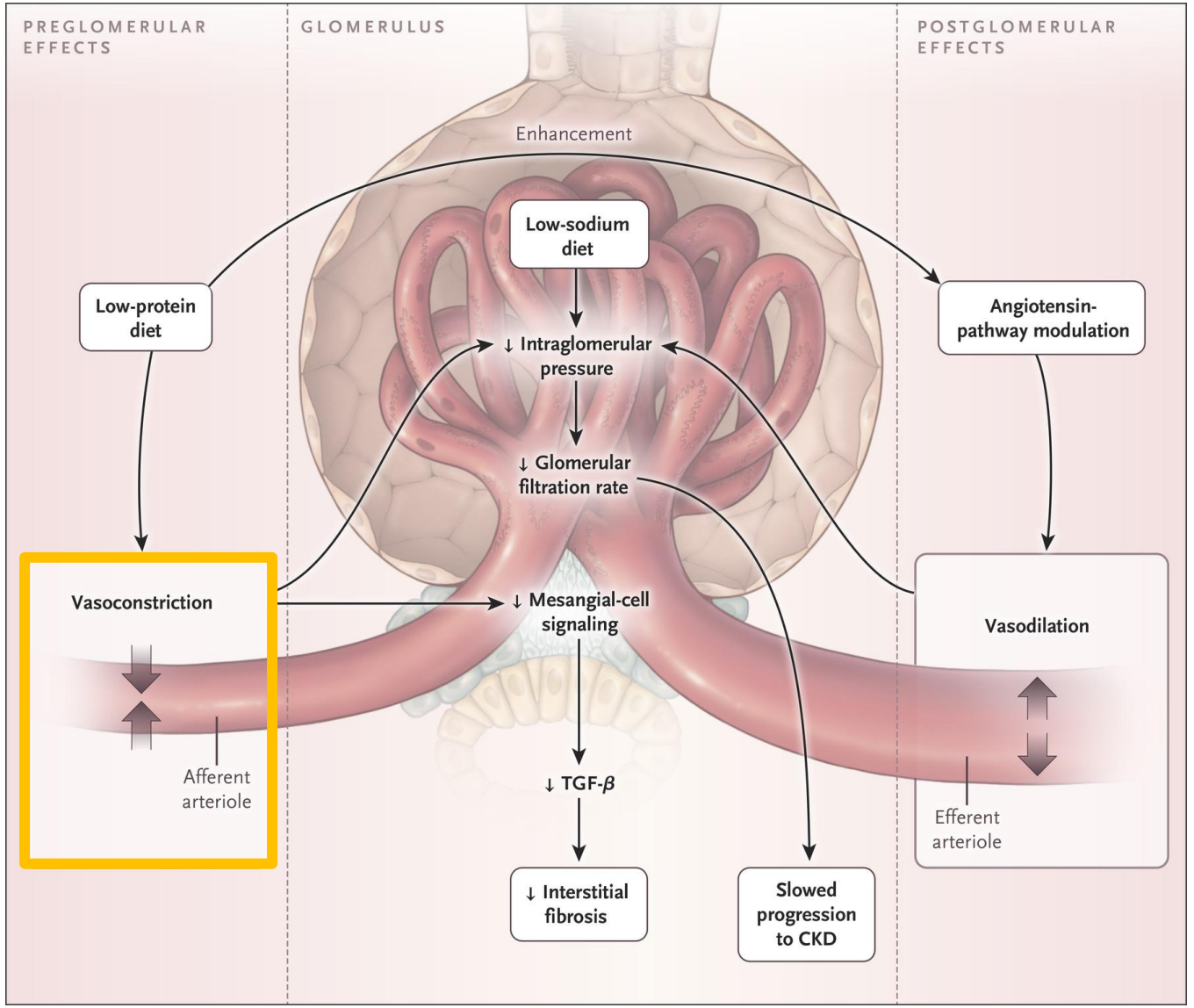
Hung SC et al. Clin Nutr 44:239–247, 2025

Mechanisms of TMA Production by Gut Microbiota



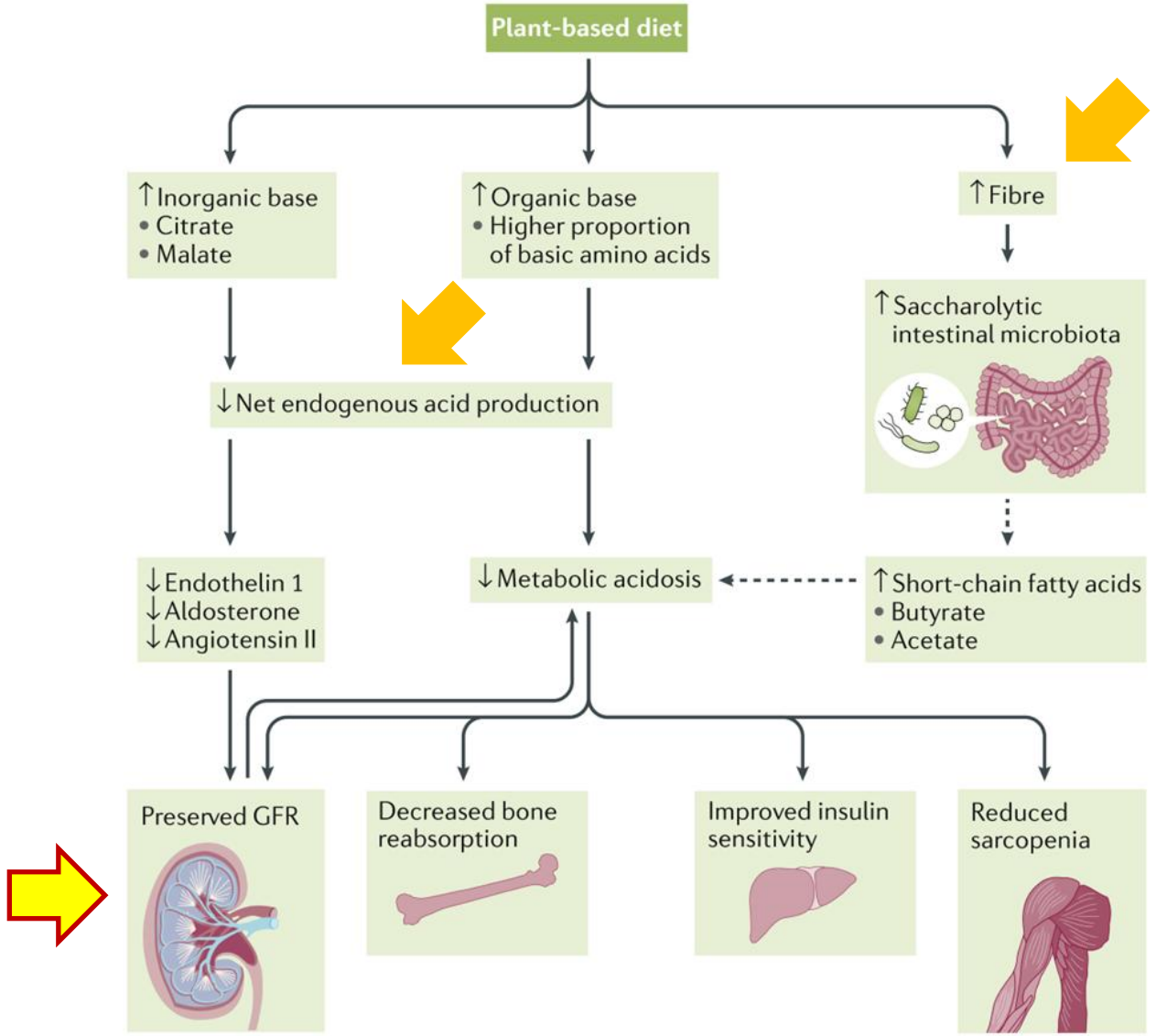
Shehata E et al. Exp Physiol 107:257–264, 2022

Effects of Low-Protein Diet on Afferent Arteriole



Kalantar-Zadeh K et al. N Engl J Med 377:1765–1776, 2017

Effects of Plant-Based Diets on CKD



Carrero JJ et al. Nat Rev Nephrol 16:525–542, 2020

Plant-Based Diets and Hyperkalemia in CKD

Plant-based foods

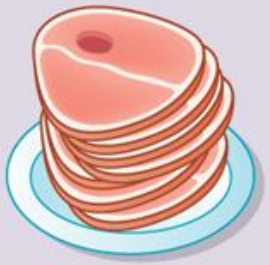
Absorption rate
50%–60%

Plant-based foods may have low absorption rate, net alkalizing effect, and carbohydrate content encourages K^+ shifts into intracellular space, minimizing impacts on serum K^+

Animal-based foods

Absorption rate
70%–90%

Animal-based protein has higher absorption and net acid effect results in higher amounts of K^+ remaining in serum



Processed foods

Absorption rate
90%

Potassium salts (often found in processed foods) absorption rate has been reported to be 90%

Kidney Int 105 (Suppl 45):S117–S314, 2024

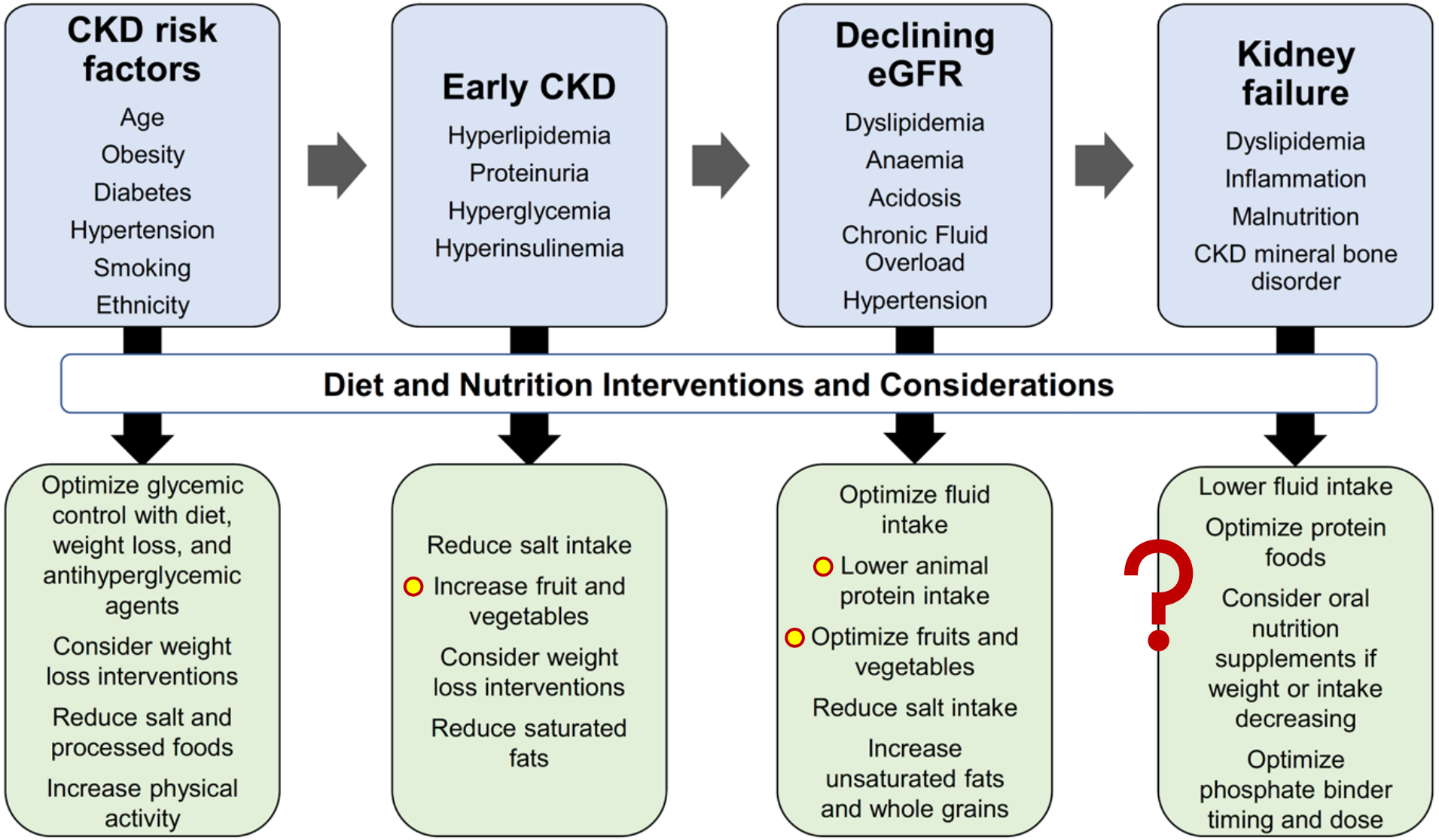


Figure 1. Chronic kidney disease spectrum with nutritional disorders and nutritional interventions considered to be important during each identified phase. Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

Healthy Plant-Based Diets and CKM Syndrome in CKD

Variable	Model 1		Model 2	
	OR (95% CI)	P value	OR (95% CI)	P value
CKM risk factors				
Overweight/obese	0.850 (0.770, 0.939)	<0.001	0.831 (0.748, 0.923)	0.001
Excess FM%	0.864 (0.789, 0.945)	0.001	0.851 (0.775, 0.934)	0.001
Central obesity	0.864 (0.790, 0.945)	0.001	0.859 (0.785, 0.940)	0.001
Hypertension	0.855 (0.764, 0.955)	0.006	0.845 (0.756, 0.945)	0.003
Triglycerides ≥150 mg/dl	0.902 (0.827, 0.983)	0.019	0.895 (0.819, 0.978)	0.015
Glucose ≥126 mg/dl	0.888 (0.805, 0.980)	0.018	0.885 (0.801, 0.978)	0.017
Malnutrition				
Hypoalbuminemia	0.836 (0.738, 0.946)	0.005	0.820 (0.718, 0.937)	0.003
Low protein intake <0.6 g/kg/day	0.883 (0.810, 0.961)	0.004	0.884 (0.811, 0.963)	0.005
Low energy intake <25 kcal/kg/day	0.815 (0.741, 0.895)	<0.001	0.812 (0.737, 0.894)	<0.001
Hyperkalemia	0.919 (0.788, 1.072)	0.284	0.905 (0.767, 1.069)	0.241

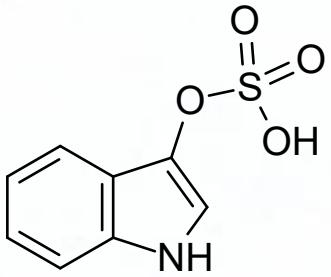
(median eGFR 23.1 mL/min/1.73 m^2)

Hung SC et al. J Am Nutr Assoc 44:651–660, 2025

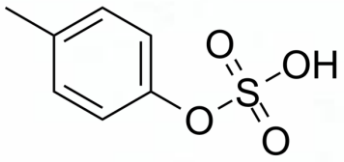
Summary 2

- Gut dysbiosis is associated with malnutrition and death in dialysis patients.
- Higher levels of TMAO is associated with faster eGFR decline in CKD. *bbuA*- or *cutC*- containing gut microbes are crucial for TMAO production and may serve as biomarkers or targets for personalized nutrition.
- In patients with advanced CKD, adherence to a healthy plant-based diet was associated with a lower risk of CKM syndrome, was more likely to achieve better nutritional status, and was not linked to an increased risk of hyperkalemia.

"Various putrefaction products of the intestine may be increased in the blood in renal insufficiency. They are phenoles, cresoles, aromatic oxyacids, and other aromatic substances."



Indoxyl sulfate

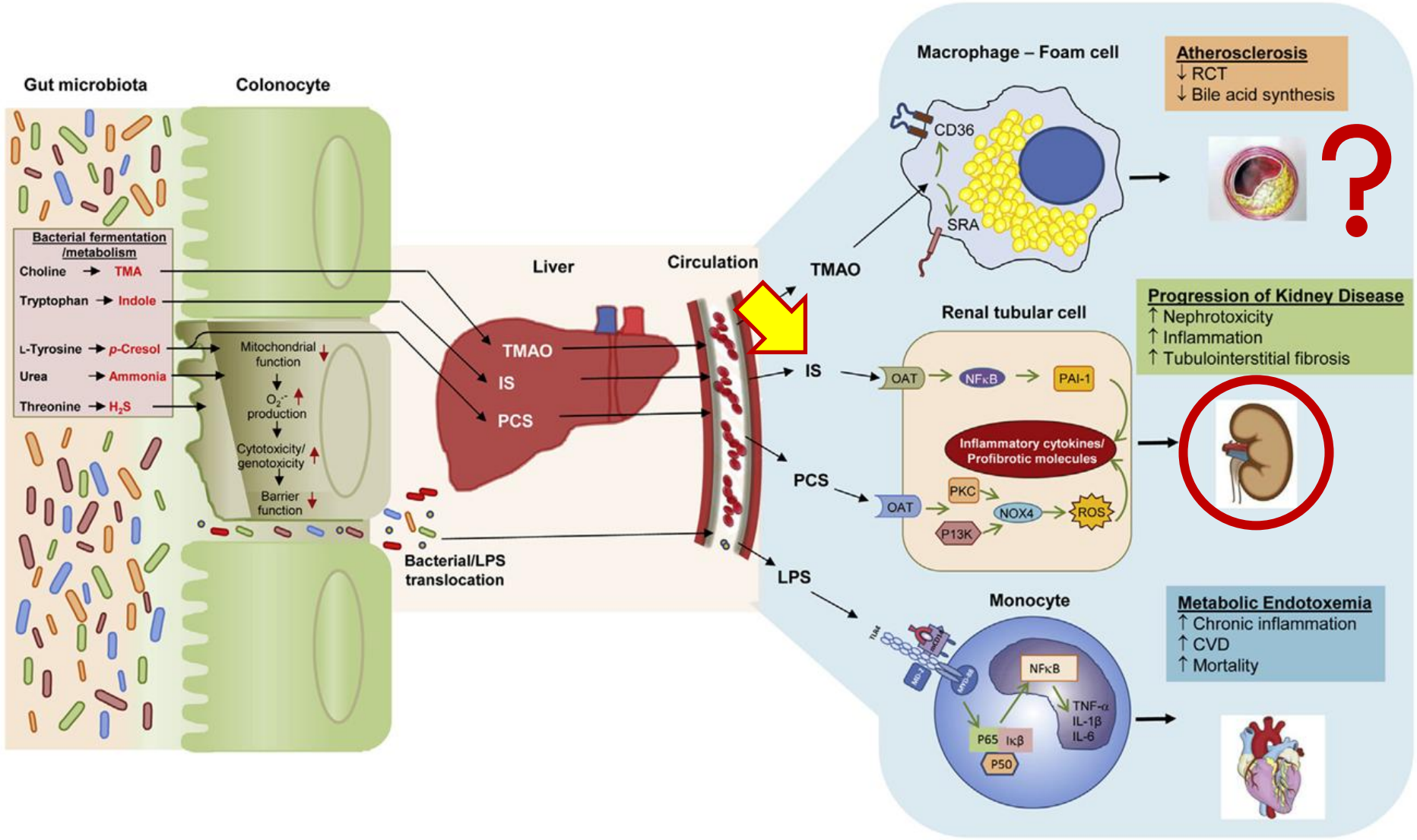


p-Cresyl sulfate

WJ Kolff

The Artificial Kidney, 1946

Gut-Derived Uremic Toxin: IS



Ramezani A et al. Am J Kidney Dis 67:483–498, 2016

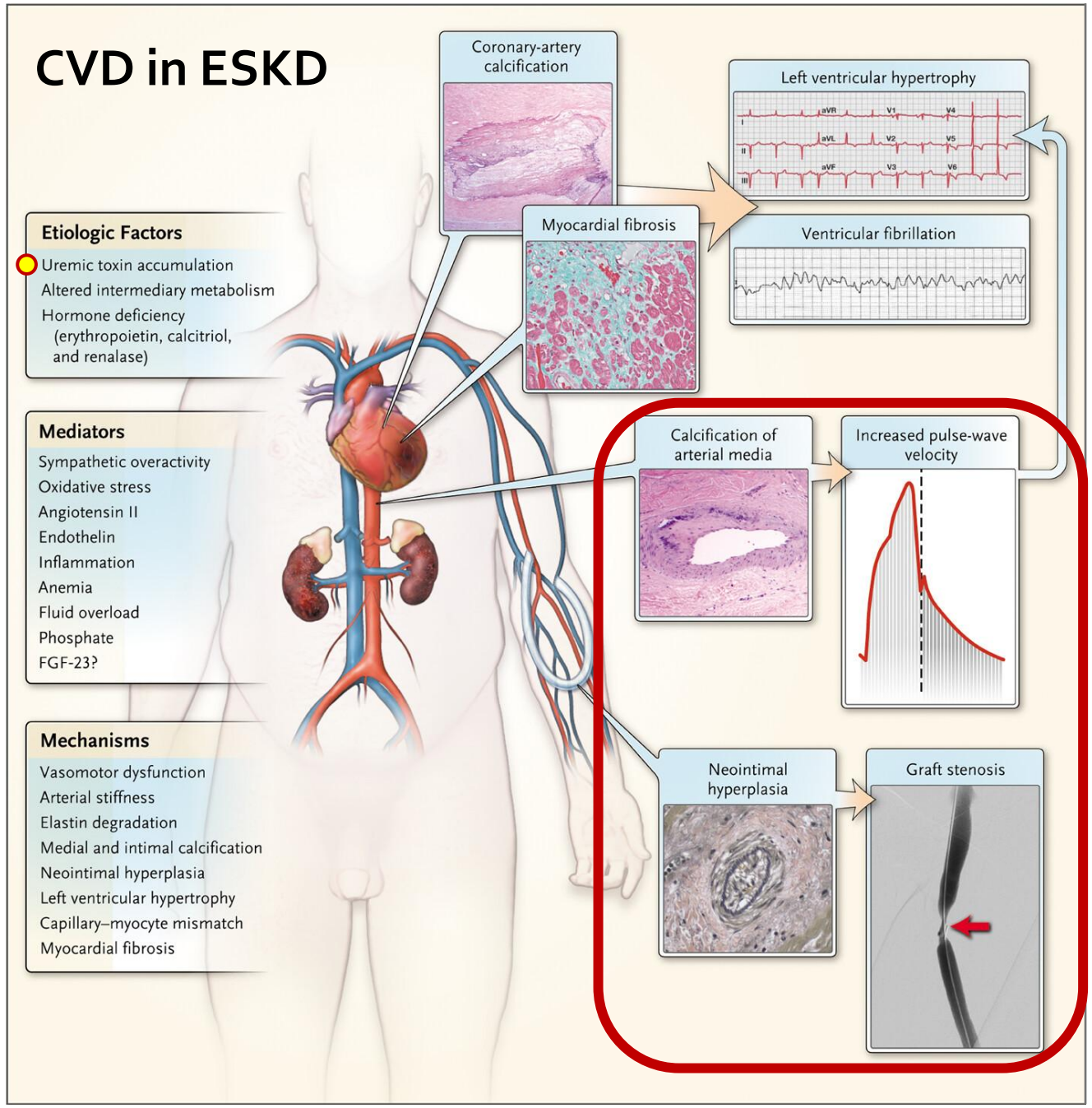
HEMO Study: PCS & IS Not Associated with CV Outcomes

Table 2 | Association of uremic solutes with outcomes in the Hemodialysis (HEMO) study

	Model 1 Unadjusted HR (95% CI)	*P*-value	Model 2 Adjusted: age, sex, race HR (95% CI)	*P*-value	Model 3 Adjusted: model 2 + comorbidity + clinical + labs + residual kidney function HR (95% CI)	*P*-value	Model 4 (final) Adjusted: model 3 + nutritional parameters HR (95% CI)	*P*-value	Model 5 (additional analyses) Adjusted: model 4 + TMAO + ADMA + SDMA HR (95% CI)	*P*-value
First CV event (events = 641; IR = 273.3)										
PCS	0.95 (0.91–0.99)	0.03	0.96 (0.92–0.99)	0.01	0.98 (0.94–1.01)	0.14	0.98 (0.94–1.02)	0.24	0.97 (0.93–1.01)	0.16
IS	0.91 (0.86–0.97)	0.005	0.95 (0.88–1.01)	0.12	0.99 (0.92–1.07)	0.8	0.99 (0.92–1.07)	0.83	0.99 (0.91–1.07)	0.74
HIPP	0.96 (0.91–1.01)	0.11	0.97 (0.93–1.02)	0.21	0.98 (0.94–1.03)	0.48	0.99 (0.95–1.04)	0.73	0.98 (0.94–1.03)	0.42
PAG	1.04 (0.97–1.11)	0.31	1.03 (0.96–1.10)	0.46	0.99 (0.92–1.05)	0.65	0.99 (0.92–1.06)	0.71	0.98 (0.91–1.05)	0.5
Any-cause death (events = 563; IR = 171.8)										
PCS	0.94 (0.89–0.99)	0.02	0.93 (0.90–0.97)	0.002	0.96 (0.92–1.00)	0.05	0.96 (0.92–1.01)	0.1	0.96 (0.92–1.01)	0.13
IS	0.88 (0.82–0.95)	<0.001	0.90 (0.83–0.97)	0.006	0.97 (0.90–1.05)	0.43	0.98 (0.91–1.06)	0.59	0.97 (0.90–1.05)	0.5
HIPP	0.96 (0.89–1.04)	0.36	0.98 (0.92–1.05)	0.58	1.03 (0.97–1.10)	0.33	1.04 (0.98–1.11)	0.17	1.04 (0.98–1.10)	0.24
PAG	1.09 (1.00–1.19)	0.04	1.09 (1.00–1.18)	0.04	1.05 (0.97–1.13)	0.21	1.06 (0.98–1.15)	0.12	1.06 (0.97–1.16)	0.17

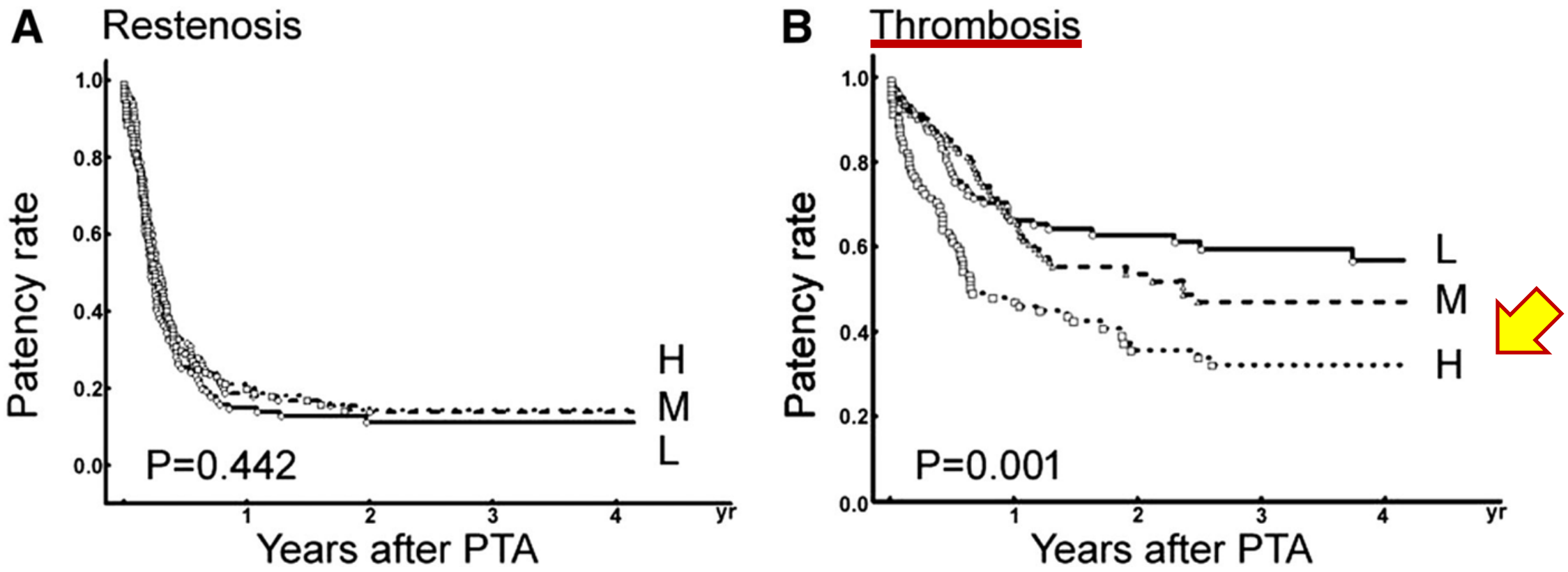
HD (*n* = 1273)

Shafi T et al. Kidney Int 92:1484–1492, 2017



Himmelfarb J et al. N Engl J Med 363:1833–1845, 2010

Indoxyl Sulfate and HD Access Thrombosis



306 patients undergoing angioplasty for dialysis access dysfunction. Median follow-up duration was 32 months. 262 (86%) had symptomatic restenosis, 153 (50%) had access thrombosis, and 25 (8%) had access failure.

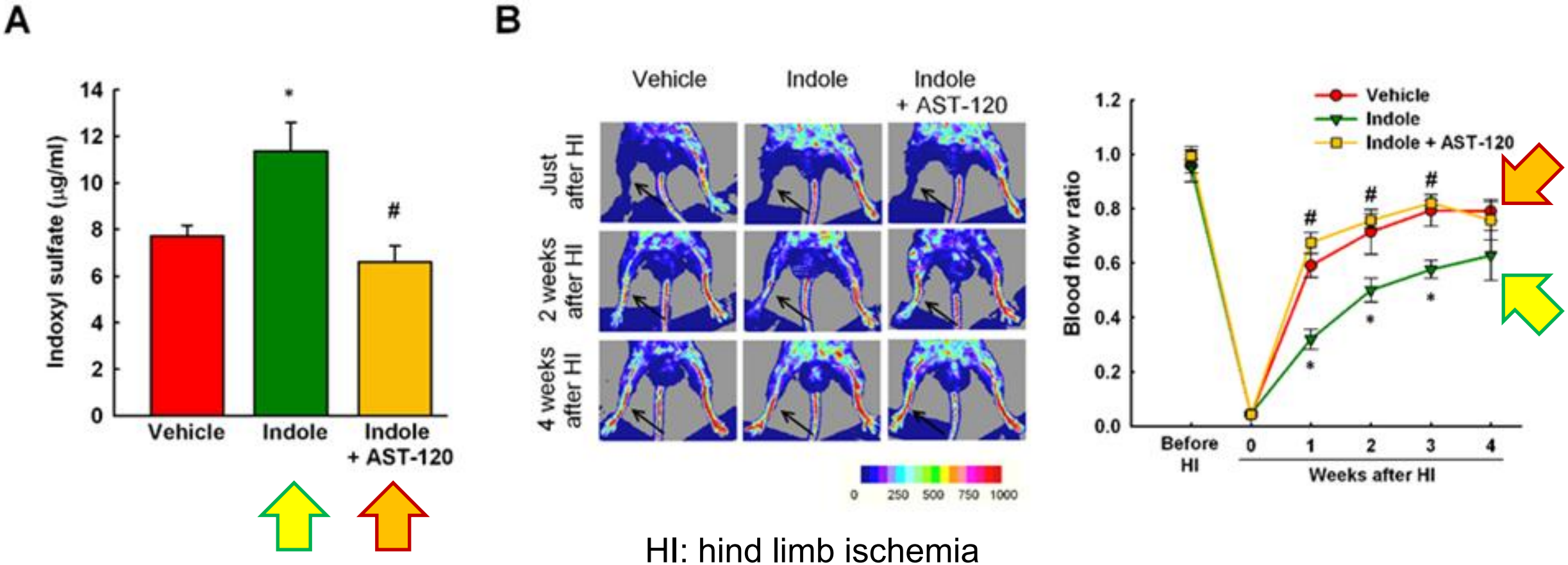
Wu CC, Hung SC et al. J Am Soc Nephrol 27:1254–1264, 2016

Indoxyl Sulfate and Incident PAD in HD Patients

Predictor	PAD	MACE	Mortality
Indoxyl sulfate (10 μg/mL increase)	**1.19 (1.05–1.35)[a]**	1.00 (0.90–1.12)	0.98 (0.90–1.07)
BMI (kg/m^2)	1.04 (0.94–1.14)	1.05 (0.97–1.14)	0.96 (0.90–1.02)
Systolic BP (10 mmHg increase)	1.08 (0.90–1.29)	1.17 (1.00–1.36)	1.04 (0.93–1.17)
TC (10 mg/dL increase)	1.04 (0.96–1.13)	1.03 (0.96–1.11)	1.01 (0.95–1.07)
HDL-C (10 mg/dL increase)	0.94 (0.75–1.17)	0.91 (0.76–1.11)	0.92 (0.79–1.07)
LDL-C (10 mg/dL increase)	1.08 (0.98–1.19)	**1.10 (1.00–1.21)[b]**	1.03 (0.96–1.11)
Triglycerides (10 mg/dL increase)	1.00 (0.97–1.03)	1.00 (0.97–1.02)	1.01 (0.99–1.03)
TC:HDL-C	1.05 (0.93–1.18)	1.01 (0.90–1.13)	0.99 (0.90–1.10)
Calcium (mg/dL)	1.04 (0.68–1.61)	**1.61 (1.15–2.27)[a]**	**1.46 (1.12–1.89)[a]**
Phosphate (mg/dL)	1.06 (0.86–1.31)	0.99 (0.81–1.22)	0.93 (0.78–1.10)
Ln CRP (mg/L)	0.91 (0.67–1.24)	1.06 (0.82–1.37)	**1.31 (1.10–1.56)[a]**

Lin TY, Hung SC et al. Toxins 12:696, 2020

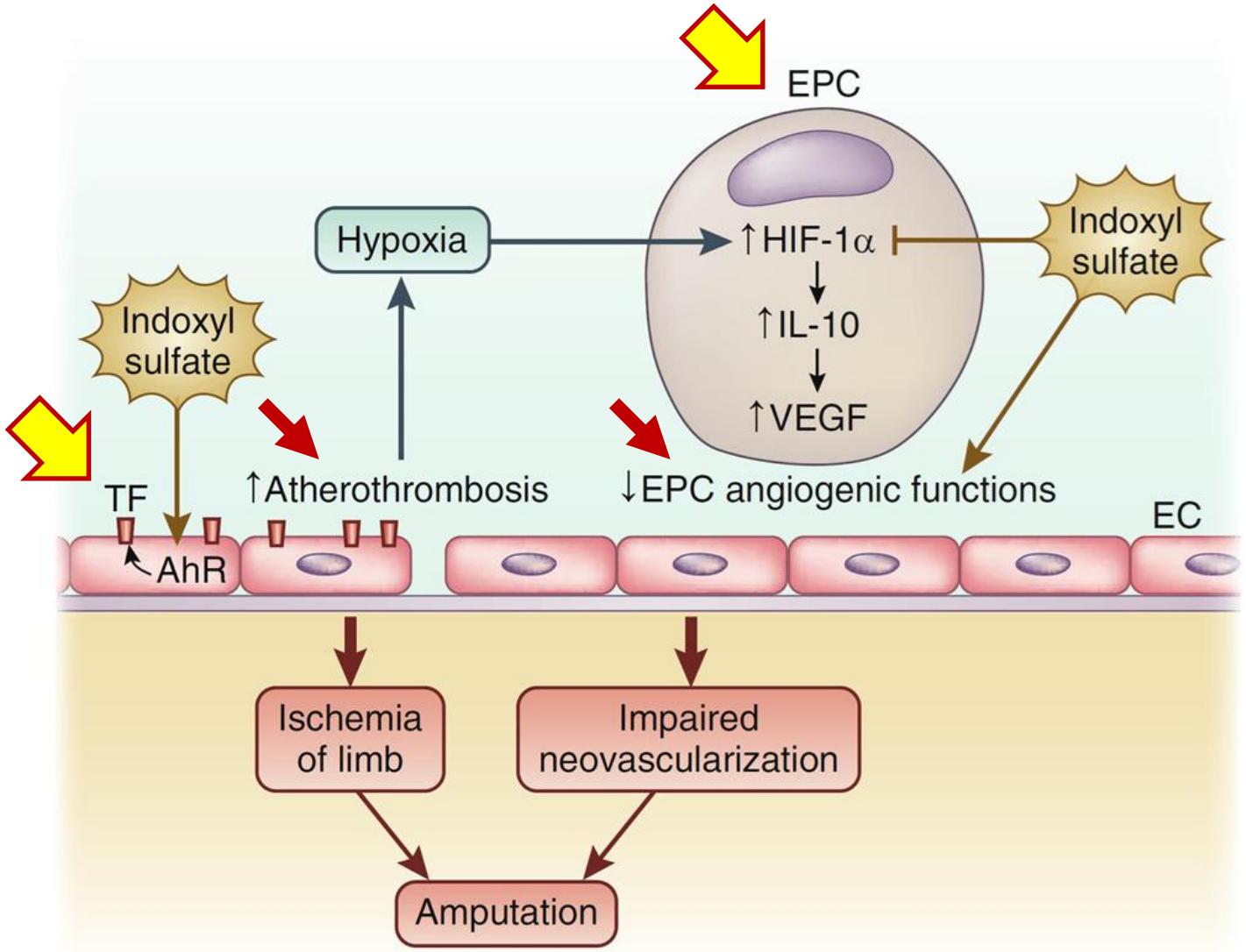
Indoxyl Sulfate and PAD in CKD Animal Models



HI: hind limb ischemia

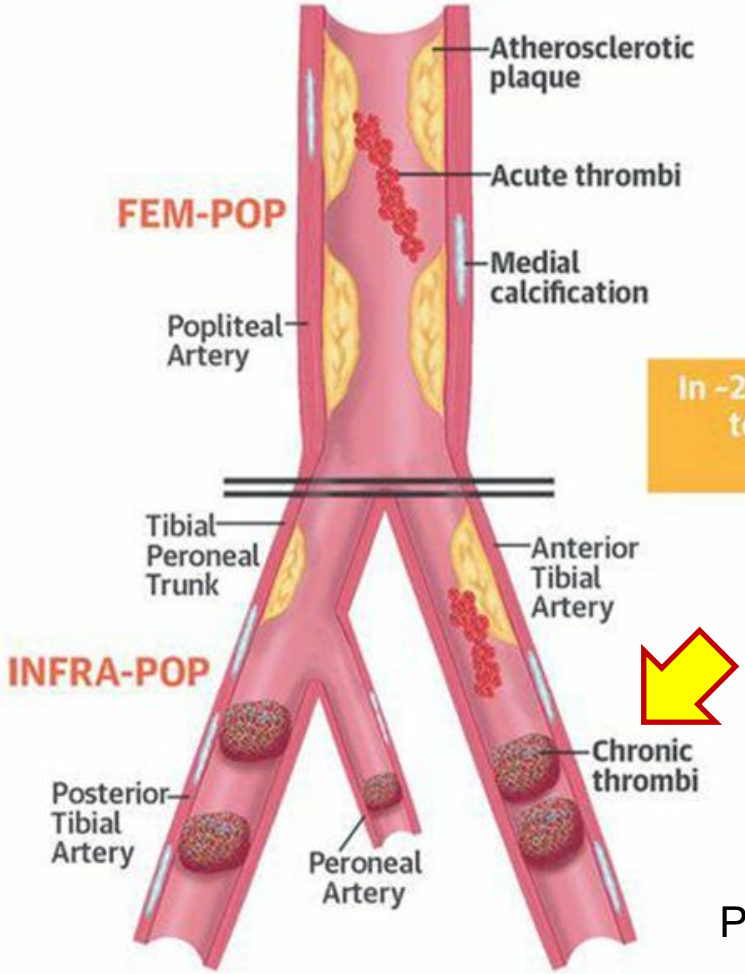
Hung SC et al. Kidney Int 89:574–585, 2016

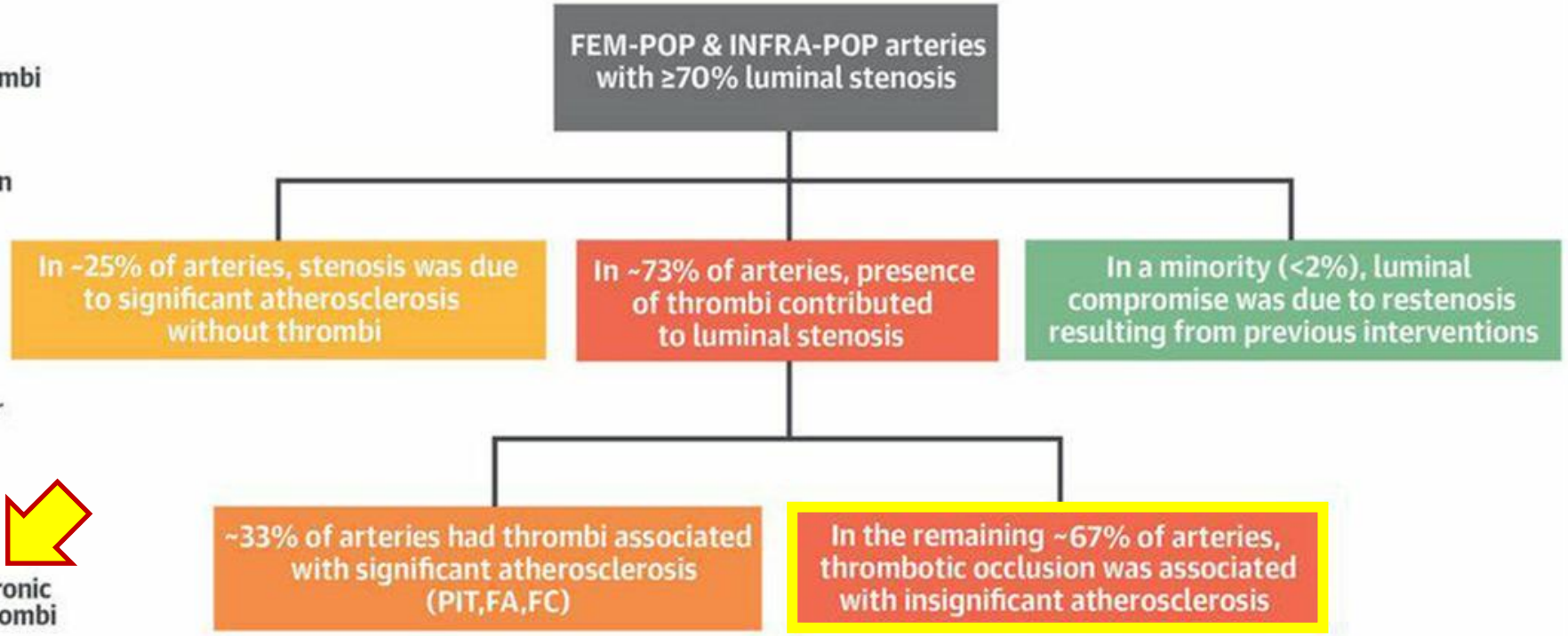
Mechanisms of Indoxyl Sulfate and PAD in CKD



Dou L et al. Kidney Int 89:532–534, 2016

CENTRAL ILLUSTRATION: Pathological Characterization of Large Arteries in Amputations for Critical Limb Ischemia

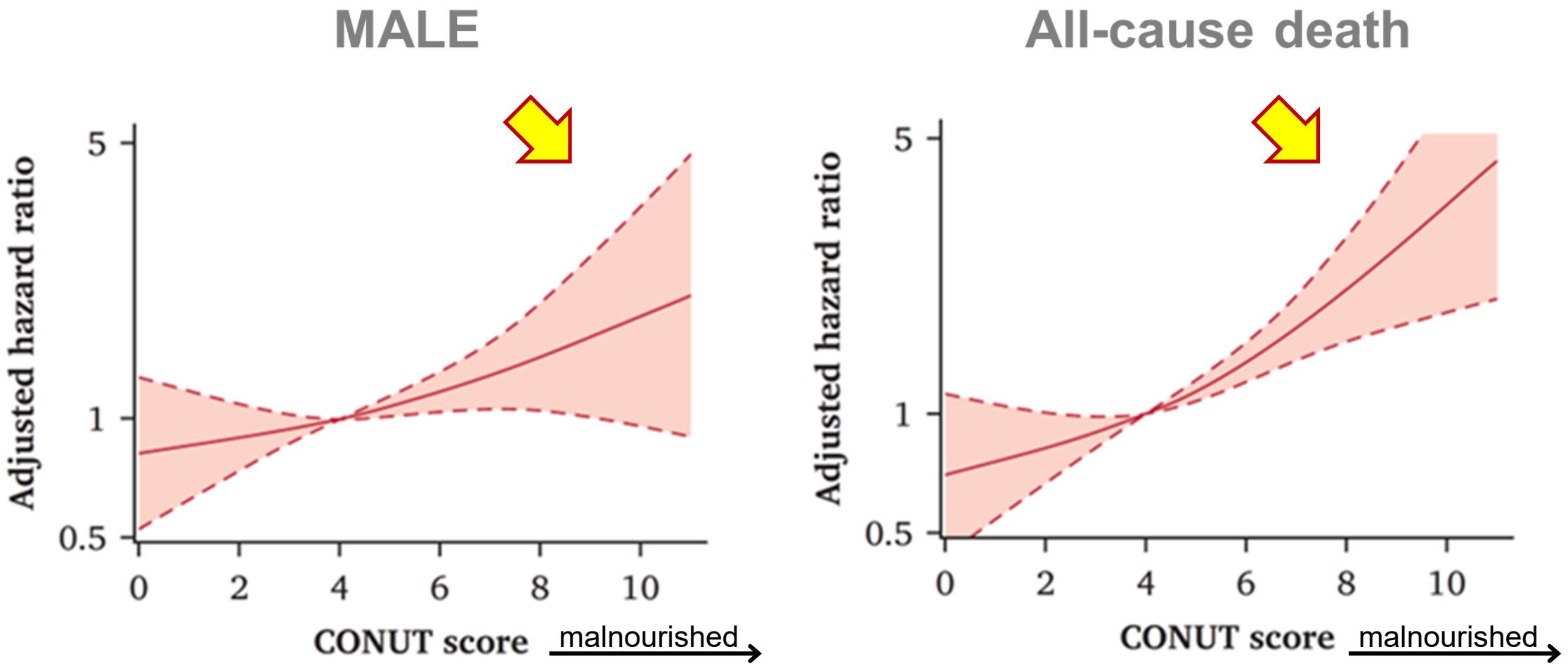




Peripheral arteries from 95 patients; 75 CLI; 20 amputations for other reasons.

Narula, N. et al. J Am Coll Cardiol. 2018;72(18):2152-63.

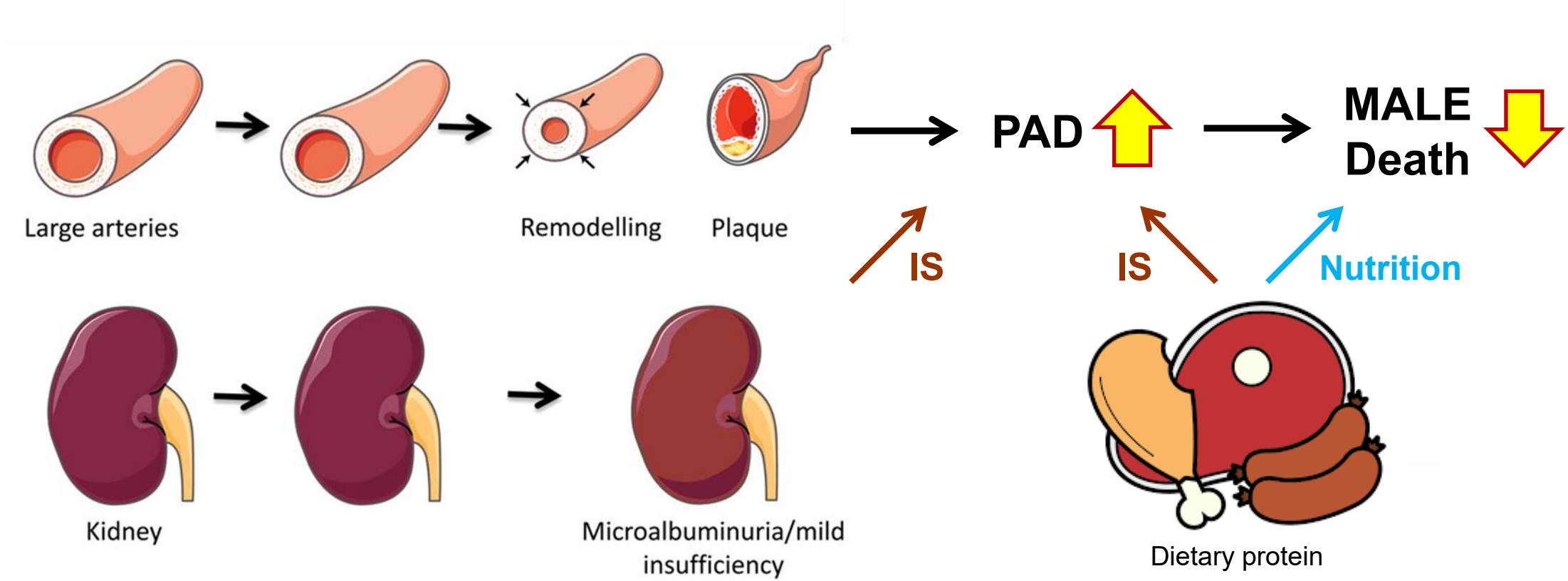
Malnutrition and Outcomes in Dialysis Patients with PAD



395 consecutive dialysis patients undergoing endovascular revascularisation for lower extremity PAD between 2005 and 2019. Adjusted by age, sex, BMI, current smoking, dialysis vintage, DM, HTN, CAD, HF, CVA, Af, use of anti-platelet agent, β-blocker, RAAS inhibitor, and statins. More than 80% of patients were malnourished, with 40.8% of patients having moderate to severe malnutrition.

Lin TY, Hung SC et al. Eur J Vasc Endovasc Surg 64:225–233, 2022

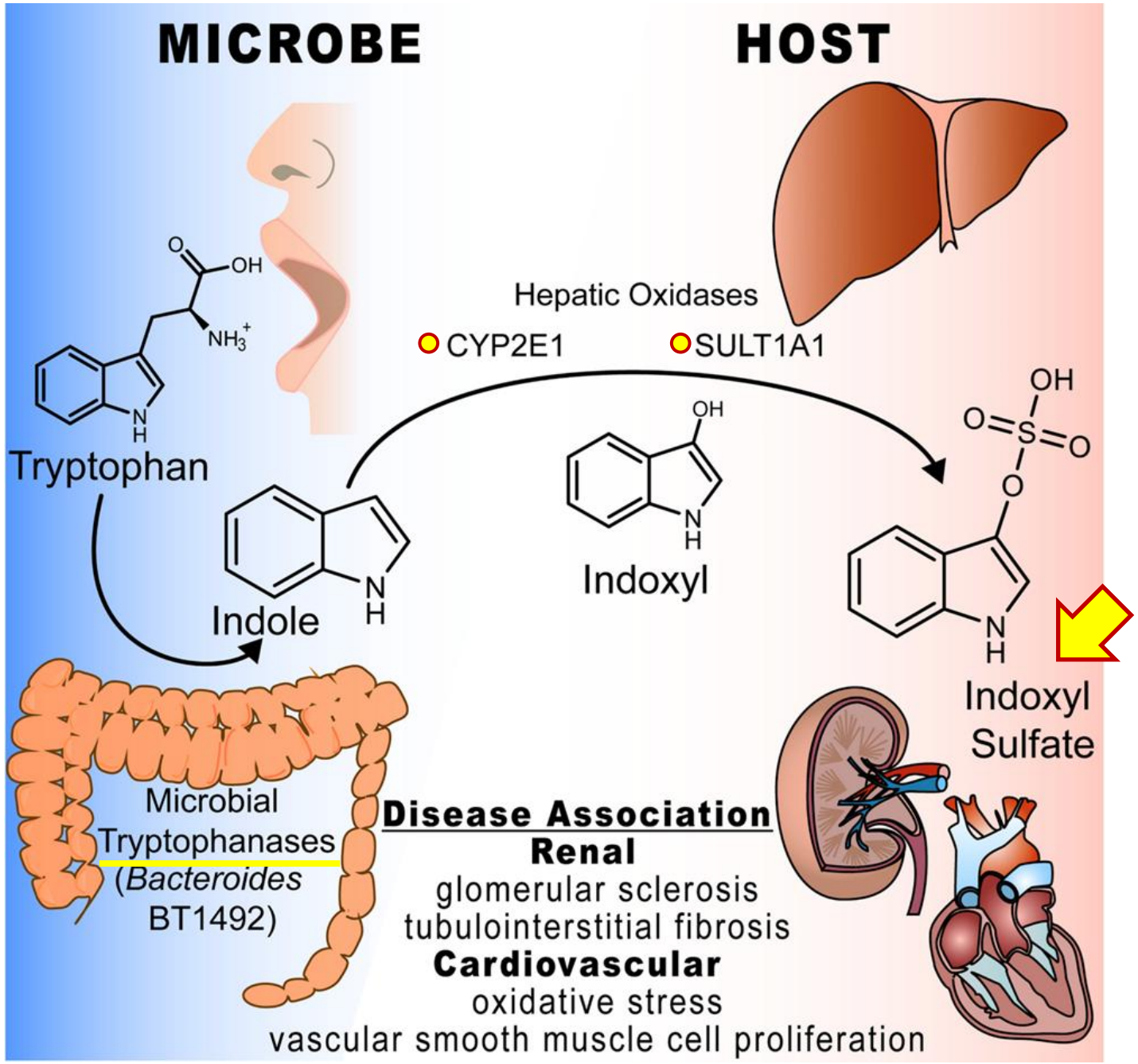
Conundrum of Nutritional Therapy in Dialysis Patients with PAD



Versari D et al. Diabetes Care 32 (Suppl 2):S314–S321, 2009

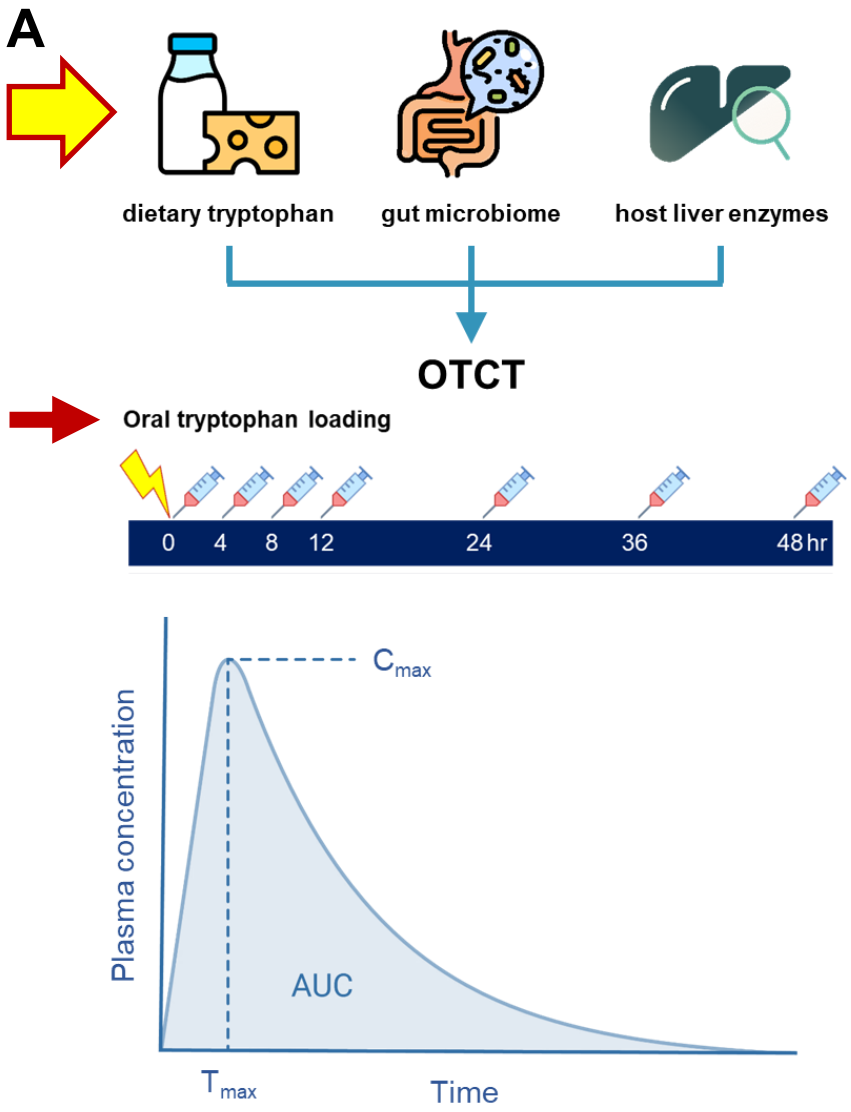
Summary 3

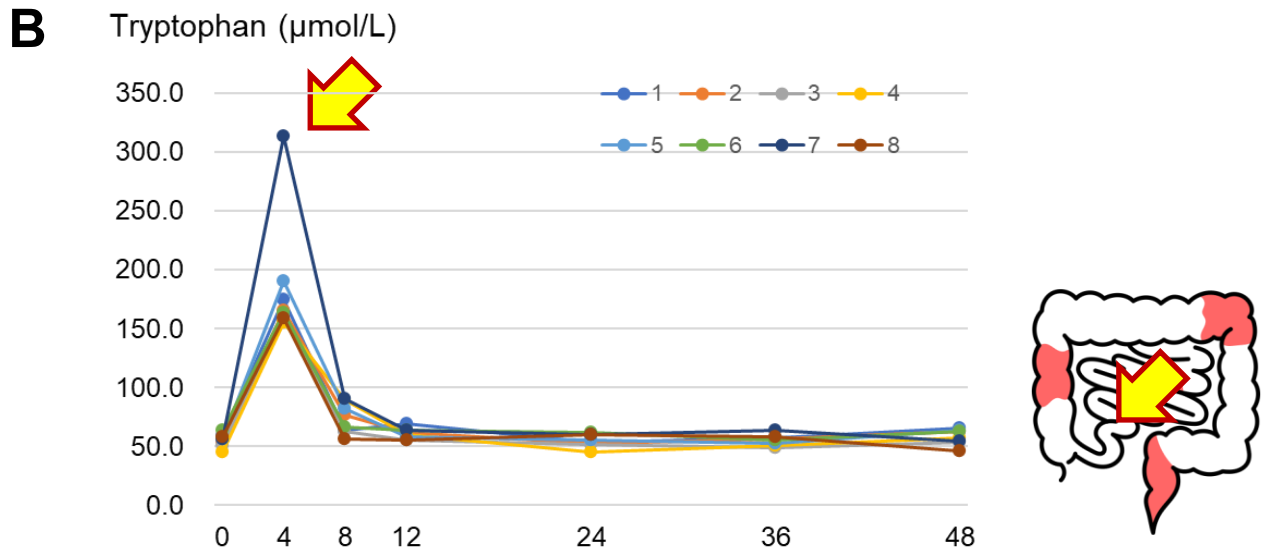
- Uremic toxins, particularly those derived from the gut microbiota, are central to complications of CKD. Among them, IS exhibits a PAD-specific vascular toxicity.
- Malnutrition markedly increases morbidity and mortality in dialysis patients undergoing endovascular therapy for PAD.
- Nutritional supplement, particularly protein rich in tryptophan, may unintentionally raise IS levels and potentially exacerbate PAD.
- Can we enhance nutritional status without increasing uremic toxin burden in CKD patients with PAD?

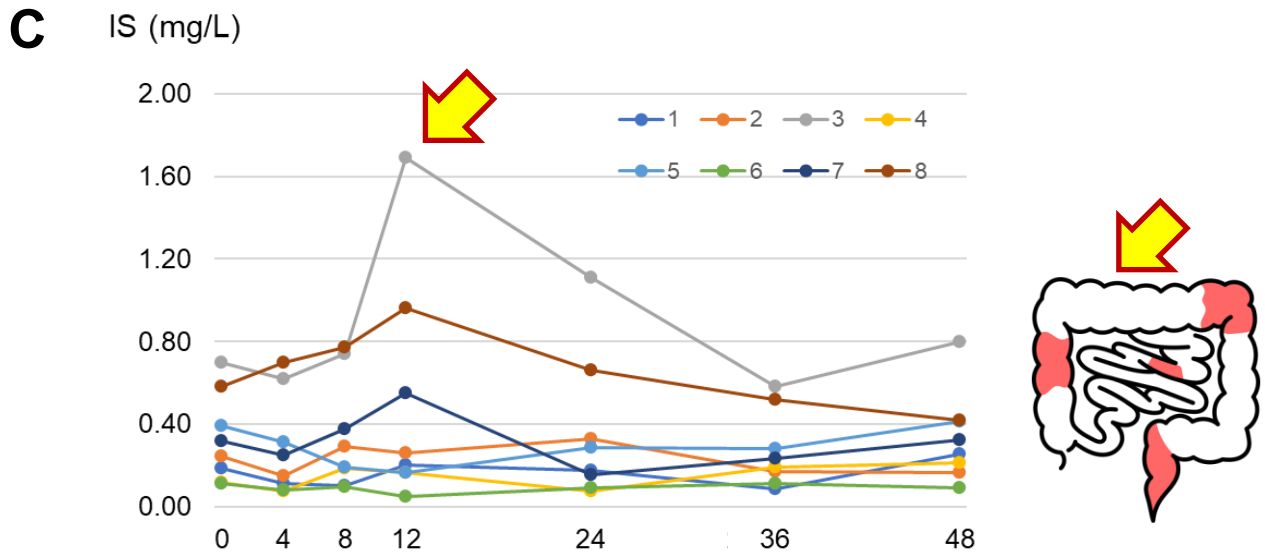


Skye SM et al. Cell Host Microbe 20:691–692, 2016

Oral Tryptophan Challenge Test (OTCT)

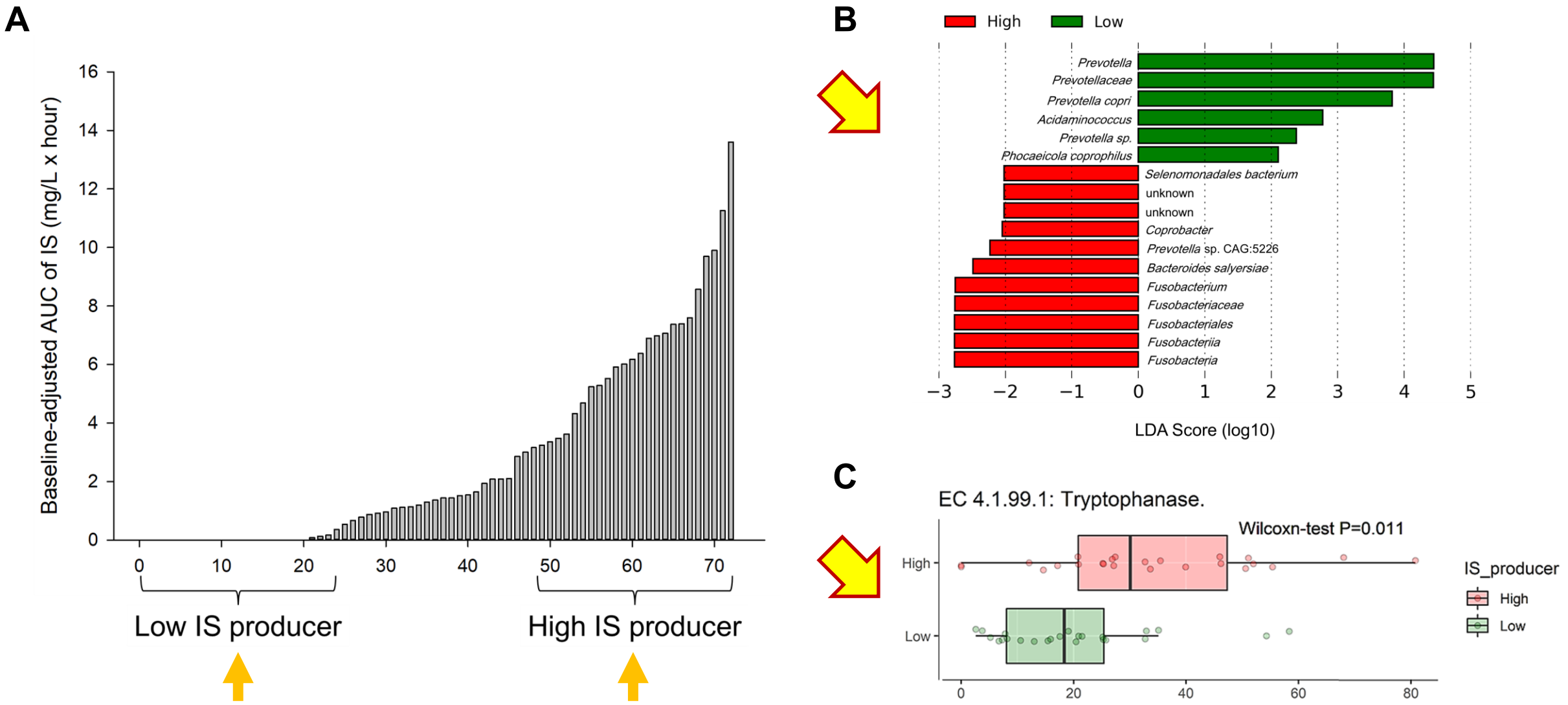




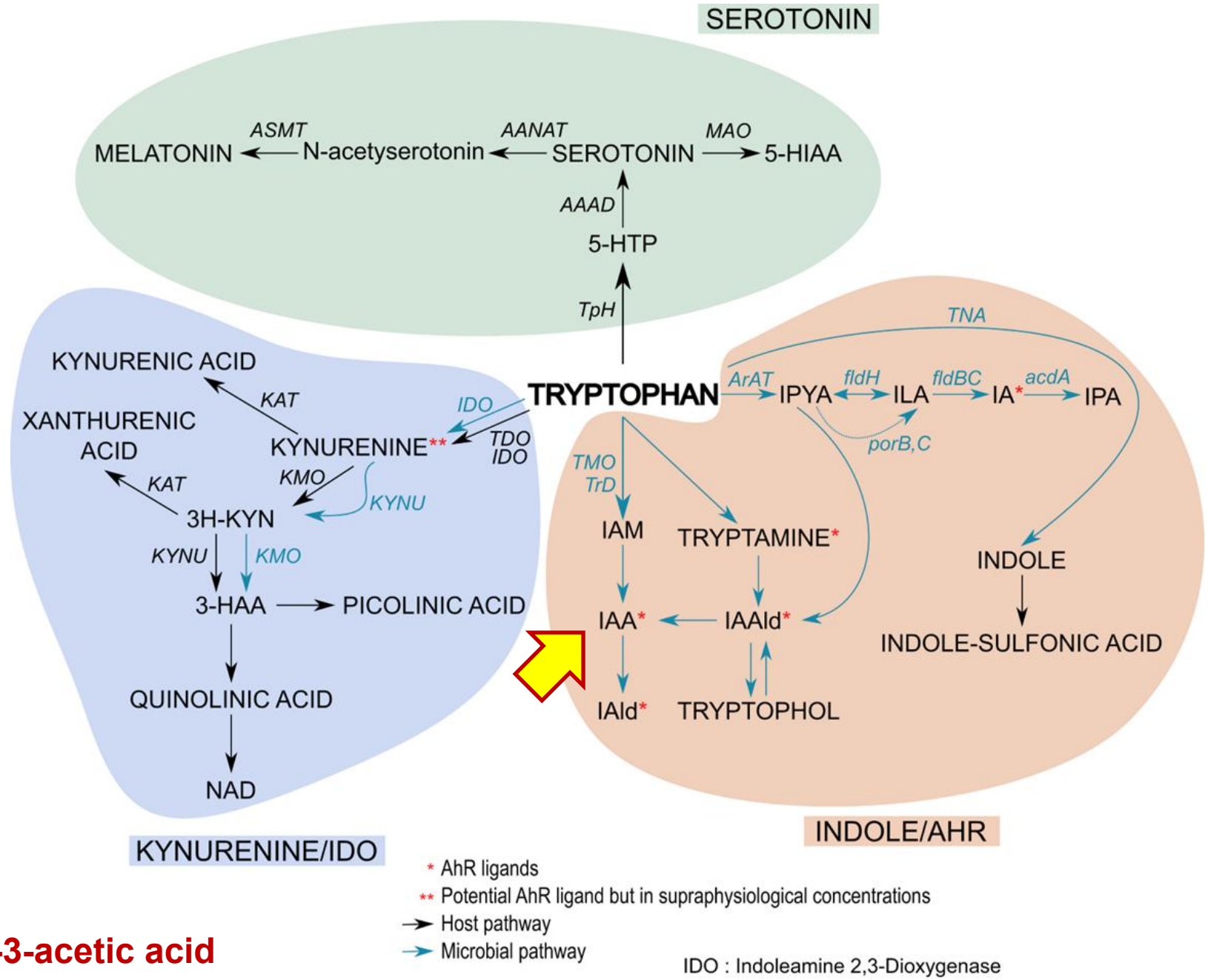


Lin TY, Hung SC et al. NPJ Biofilms Microbiomes 11:15, 2025

High Interindividual Variability of IS Production by OTCT



Lin TY, Hung SC et al. NPJ Biofilms Microbiomes 11:15, 2025



IAA: indole-3-acetic acid

Agus A et al. Cell Host Microbe 23:716–724, 2018

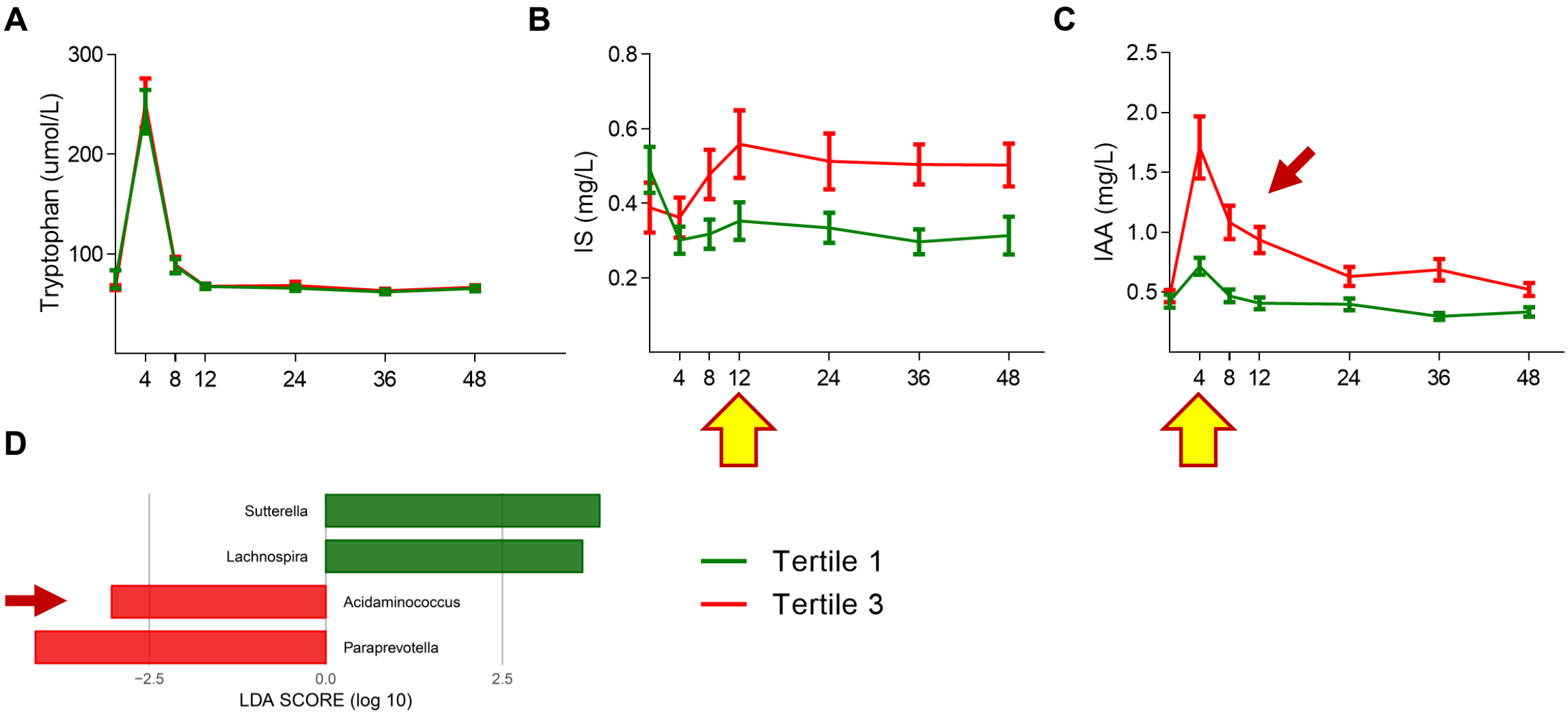
IAA and Clinical Outcomes in CKD

Patient Survival (Event 29/120)	RR (95% CI)	*P* Value
Indole-3 acetic acid	2.04 (1.05 to 3.95)	0.03
Indoxyl sulfate	1.05 (0.95 to 1.16)	<0.4
p-cresyl sulfate	1.05 (0.97 to 1.12)	0.21
Major CV Event (Event 35/120)	**RR (95% CI)**	***P* Value**
Indole-3 acetic acid	1.95 (1.09 to 3.50)	0.03
Indoxyl sulfate	0.99 (0.90 to 1.08)	<0.8
p-cresyl sulfate	1.03 (0.96 to 1.10)	<0.4

(mean eGFR 26 mL/min/1.73 m^2)

Dou L et al. J Am Soc Nephrol 26:876–887, 2015

Comparison of Plasma IS and IAA During the OTCT



Lin TY, Hung SC et al. NPJ Biofilms Microbiomes 11:15, 2025

Colonic Contribution to Uremic Solutes

Solute Name	Colectomy/with Colon	*P* Value
PCS	0.01	Not detectable in colectomy
α-N-phenylacetyl-L-glutamine	0.07	<0.05
IS	0.02	<0.05
indoxyl glucuronide	0.02	<0.10
HIPP	0.28	>0.4
IAA	**0.57**	**>0.4**
indolelactic acid	1.8	>0.4
L-kynurenine	2.0	>0.4

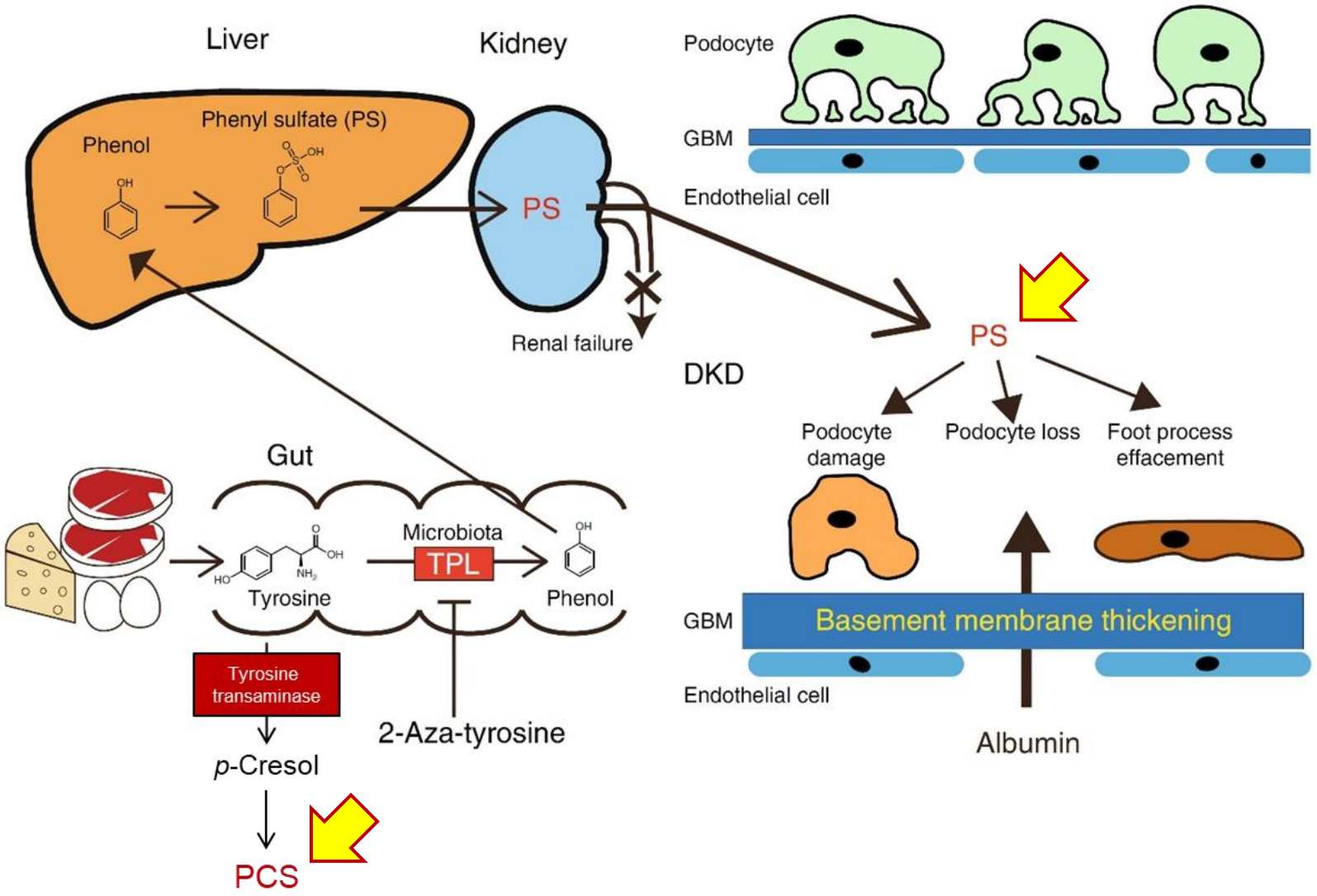
6 HD patients with total colectomy versus 9 HD patients with intact colon

Aronov PA et al. J Am Soc Nephrol 22:1769–1776, 2011

Summary 4

- Responses to nutritional therapy depend on its interactions with gut microbiome and host genome.
- Current food-based dietary guidelines are not yet microbiome-oriented.
- The results of OTCT can serve as a personalized dietary guidance for patients with CKD. High IS/IAA producers should avoid consuming foods that contain high levels of tryptophan.
- Nephrocentric and nutricentric views of nutritional management in CKD can be integrated by applying this precision medicine approach.

Gut Microbiome-Derived PCS and PS



Kikuchi K et al. Nat Commun 10:1835, 2019

Circulation

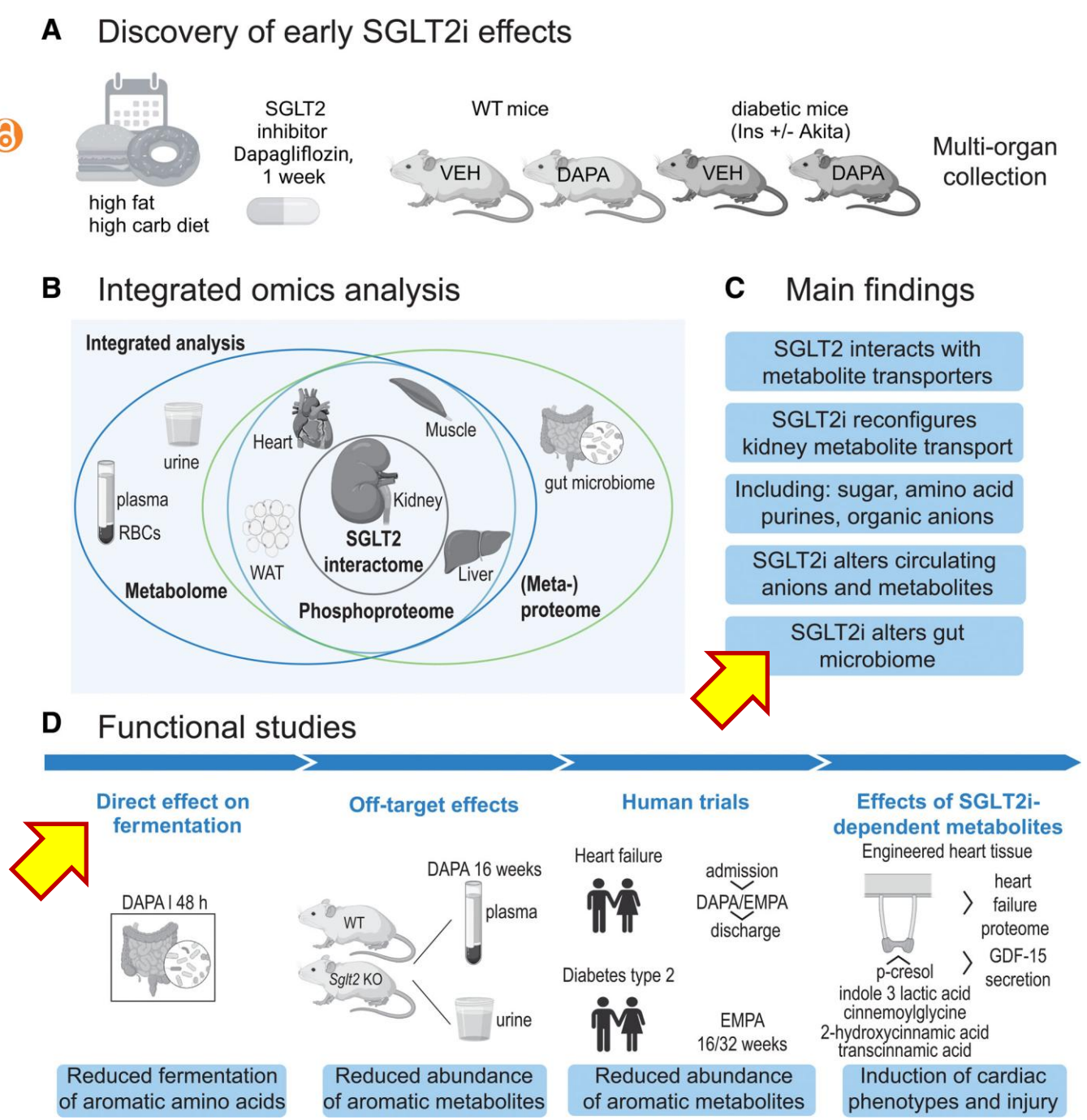
ORIGINAL RESEARCH ARTICLE

Metabolic Communication by SGLT2 Inhibition

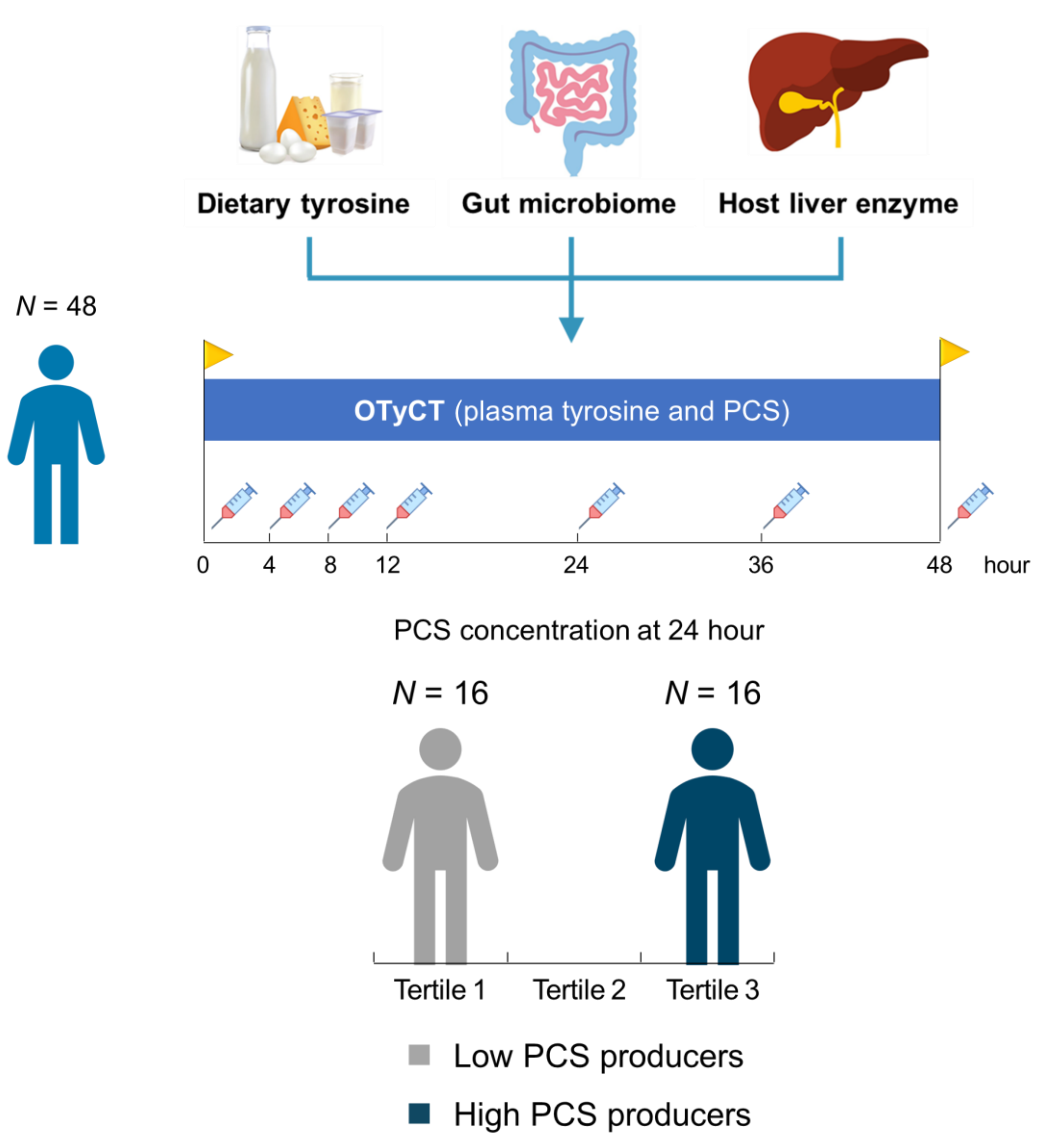
Anja M. Billing, PhD; Young Chul Kim, PhD; Søren Gullaksen, MD; Benedikt Schrage, MD, PhD; Janice Raabe, PhD; Arvid Hutzfeldt, MSc; Fatih Demir, PhD; Elina Kovalenko, MSc; Moritz Lassé, PhD; Aurelien Dugourd, PhD; Robin Fallegger, MSc; Birgit Klampe; Johannes Jaegers, PhD; Qing Li, PhD; Olha Kravtsova, PhD; Maria Crespo-Masip, PhD; Amelia Palermo, PhD; Robert A. Fenton, PhD; Elion Hoxha, MD; Stefan Blankenberg, MD; Paulus Kirchhof, MD; Tobias B. Huber, MD; Esben Laugesen, MD; Tanja Zeller, PhD; Maria Chrysopoulou, MSc; Julio Saez-Rodriguez, PhD; Christina Magnussen; Thomas Eschenhagen, MD; Alexander Staruschenko, PhD; Gary Siuzdak, PhD; Per L. Poulsen, MD; Clarissa Schwab, PhD; Friederike Cuello, PhD; Volker Vallon, MD*; Markus M. Rinschen, MD*

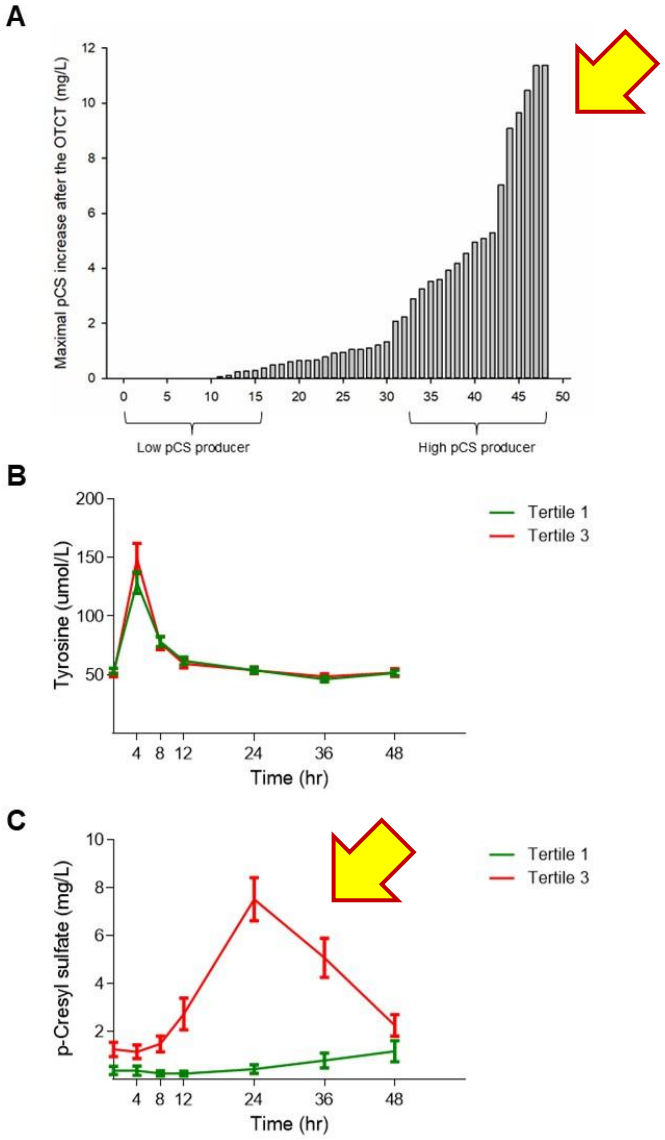
SGLT2i reduced microbiome formation of uremic toxins such as p-cresol sulfate and thereby their body exposure and need for renal detoxification, which, combined with direct kidney effects of SGLT2i, including less proximal tubule glucotoxicity and a broad downregulation of apical transporters (including sodium, amino acid, and urate uptake), provides a metabolic foundation for kidney and cardiovascular protection.

Billing AM et al. Circulation 149:860–884, 2024



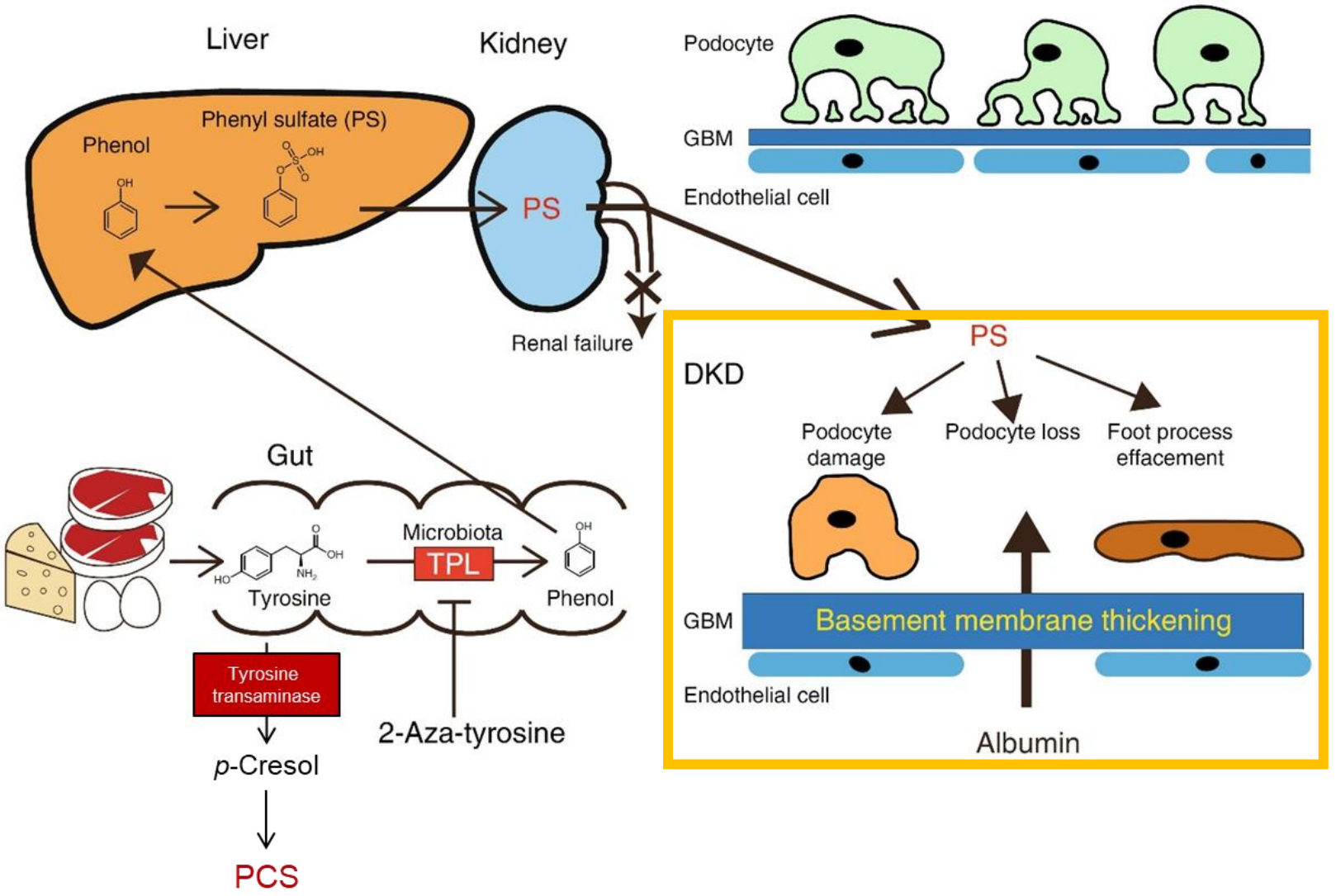
Oral Tyrosine Challenge Test (OTyCT)





High IS/PCS producers

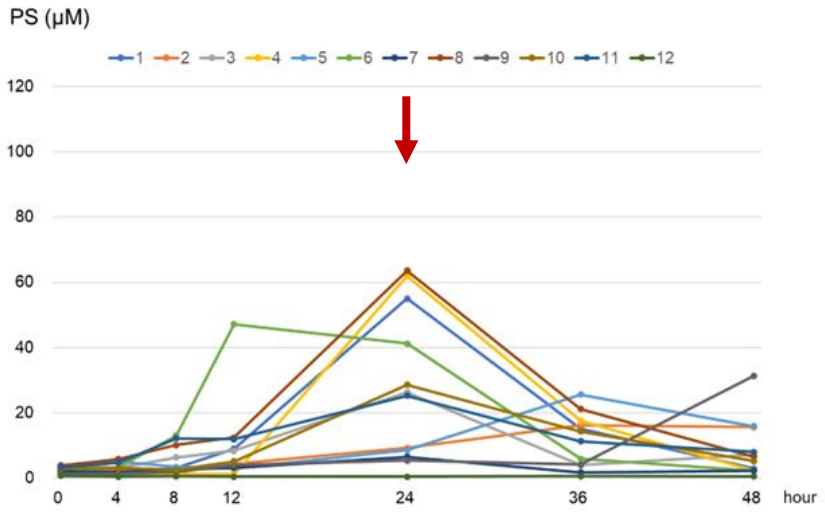
Gut Microbiome-Derived PS and DKD

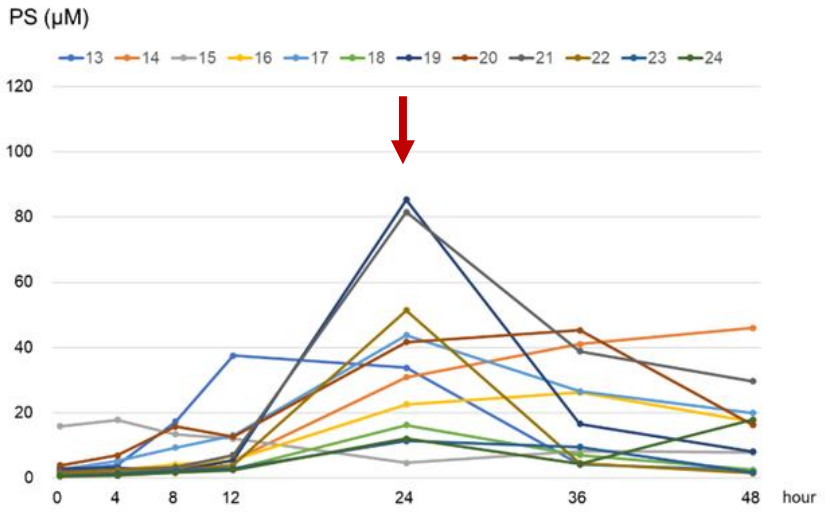


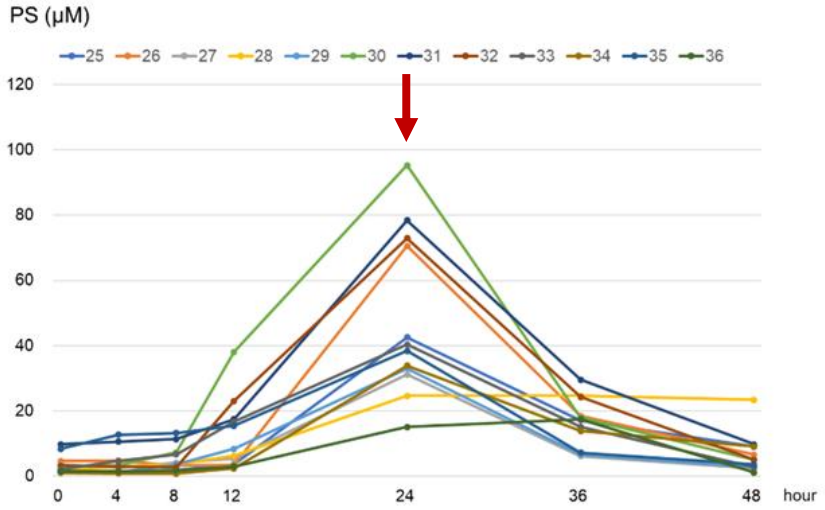
阿部高明

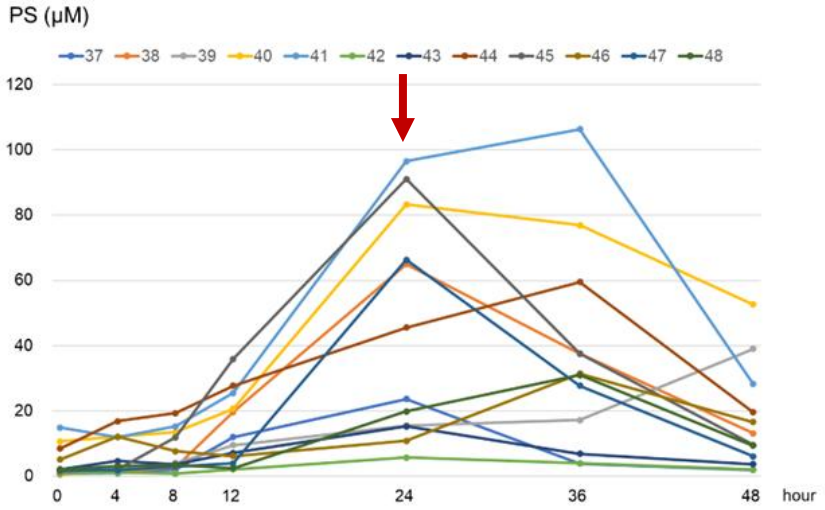
Kikuchi K et al. Nat Commun 10:1835, 2019

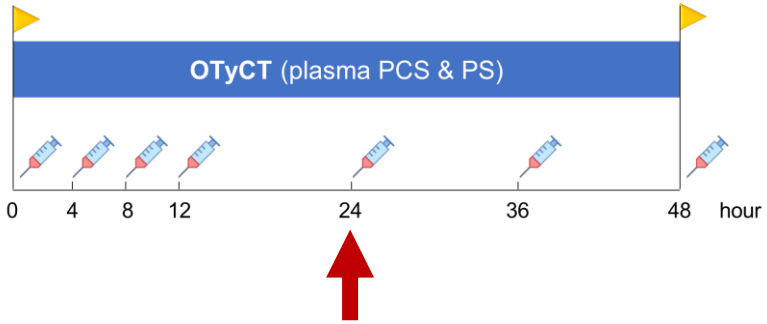
Plasma PS in Oral Tyrosine Challenge Test







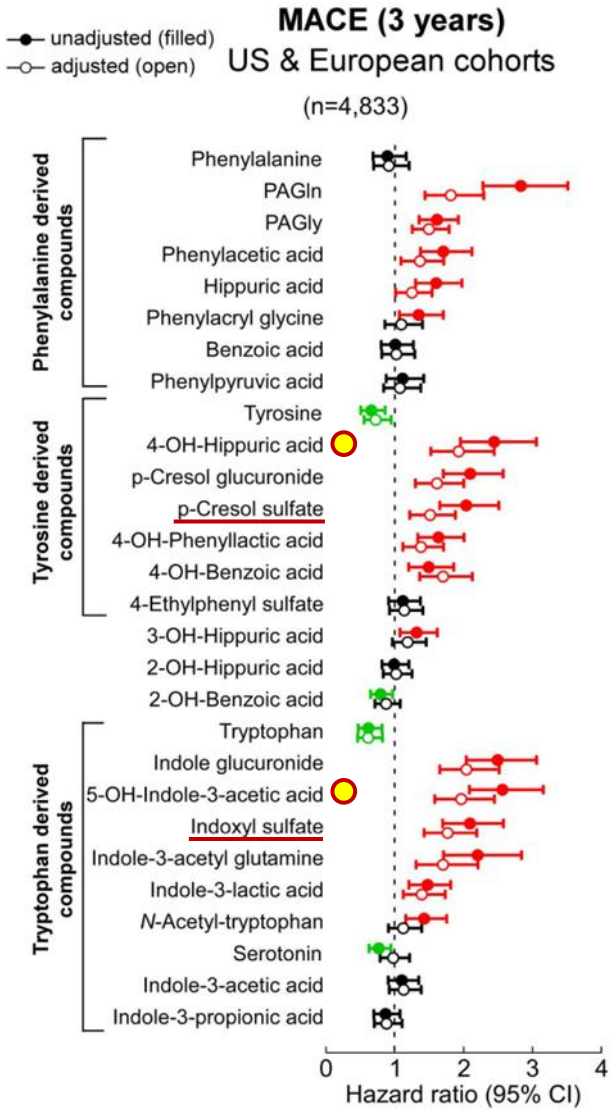


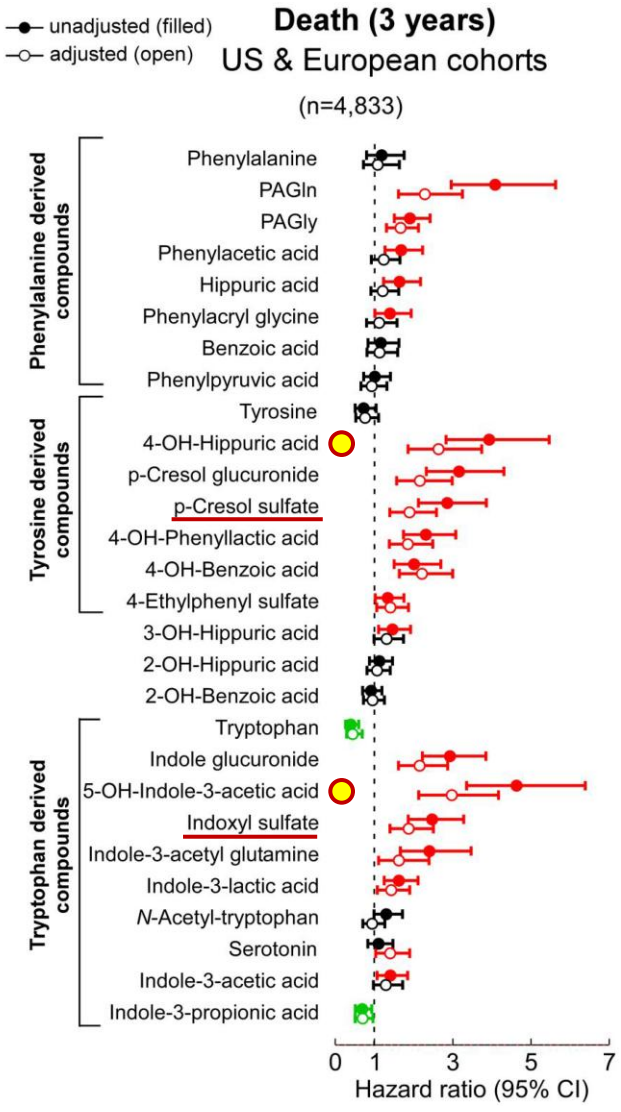


Hung SC et al. 2025

Plasma Metabolites and Risk of CV Morbidity and Mortality

Characteristics	All participants (*n*=4833)
Age (years)	64.9 (56.1–73.5)
Male sex (%)	65.4
Smoking (%)	13.4
Hypertension (%)	46.0
Diabetes (%)	30.9
CAD (%)	76.2
MACE at 3 years, (%)	14.7
HDL (mg/dL)	35.7 (29.3–44.3)
LDL (mg/dL)	95.0 (76.0–117.0)
TG (mg/dL)	119.0 (87.0–166.0)
hsCRP (mg/L)	2.34 (1.00–5.73)
eGFR (mL/min/1.73 m^2)	88.76 (71.97–99.13)
Baseline medications (%)	
Aspirin (%)	70.7
ACE inhibitors (%)	53.6
Beta blocker (%)	62.3
Statin (%)	60.1

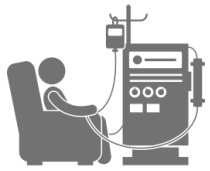




Nemet I et al. Eur Heart J 44:3085–3096, 2023

Plasma Metabolites and Risk of Mortality in HD Patients

	Crude		Model 1		Model 2	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Tyrosine*	1.55 (0.86–2.79)	0.147	1.20 (0.61–2.37)	0.602	1.05 (0.47–2.32)	0.912
Tyrosine (Q4 vs. Q1)	1.58 (0.92–2.73)	0.101	1.11 (0.63–1.97)	0.729	1.09 (0.49–2.43)	0.830
4-OH-Hippuric acid*	**1.21 (0.89–1.63)**	**0.228**	**1.54 (1.13–2.11)**	**0.007**	**1.65 (1.08–2.53)**	**0.022**
4-OH-Hippuric acid (Q4 vs. Q1)	**1.42 (0.79–2.52)**	**0.240**	**2.14 (1.14–3.99)**	**0.017**	**2.57 (1.07–6.16)**	**0.035**
p-Cresol glucuronide*	1.09 (0.93–1.28)	0.299	1.12 (0.95–1.31)	0.191	1.30 (1.03–1.65)	0.028
p-Cresol glucuronide (Q4 vs. Q1)	1.37 (0.77–2.43)	0.282	1.46 (0.82–2.60)	0.203	2.47 (0.99–6.14)	0.052
p-Cresol sulfate*	1.02 (0.82–1.26)	0.864	1.01 (0.82–1.24)	0.932	1.18 (0.87–1.60)	0.289
p-Cresol sulfate (Q4 vs. Q1)	1.40 (0.76–2.58)	0.281	1.39 (0.75–2.58)	0.301	2.95 (1.17–7.42)	0.021
4-OH Phenyllactic acid*	1.65 (1.09–2.49)	0.018	1.70 (1.12–2.60)	0.013	1.27 (0.72–2.25)	0.412
4-OH Phenyllactic acid (Q4 vs. Q1)	1.97 (1.05–3.70)	0.036	1.93 (1.01–3.69)	0.046	1.67 (0.69–4.02)	0.254
4-OH-Benzoic acid*	1.18 (0.92–1.52)	0.185	1.18 (0.92–1.51)	0.190	1.65 (1.03–2.66)	0.037
4-OH-Benzoic acid (Q4 vs. Q1)	1.75 (0.96–3.18)	0.069	1.75 (0.95–3.22)	0.073	2.30 (1.01–5.25)	0.048
4-Ethylphenyl sulfate*	1.11 (0.93–1.32)	0.237	1.01 (0.85–1.21)	0.913	1.12 (0.89–1.40)	0.338
4-Ethylphenyl sulfate (Q4 vs. Q1)	1.40 (0.76–2.56)	0.280	0.96 (0.50–1.85)	0.909	1.23 (0.56–2.70)	0.612
3-OH-Hippuric acid*	0.82 (0.68–0.98)	0.030	0.90 (0.74–1.10)	0.323	0.93 (0.73–1.18)	0.528
3-OH-Hippuric acid (Q4 vs. Q1)	0.76 (0.44–1.31)	0.326	1.08 (0.61–1.94)	0.785	1.11 (0.55–2.26)	0.776
2-OH-Hippuric acid*	1.07 (0.97–1.19)	0.182	1.09 (0.98–1.20)	0.116	1.08 (0.95–1.23)	0.256
2-OH-Hippuric acid (Q4 vs. Q1)	1.30 (0.77–2.19)	0.333	1.46 (0.85–2.50)	0.171	1.64 (0.78–3.46)	0.192
2-OH-Benzoic acid*	1.10 (0.97–1.24)	0.146	1.07 (0.94–1.21)	0.328	1.16 (0.97–1.38)	0.101
2-OH-Benzoic acid (Q4 vs. Q1)	1.99 (1.02–3.88)	0.043	1.87 (0.94–3.72)	0.077	2.30 (0.81–6.50)	0.116
Phenyl sulfate*	0.82 (0.63–1.05)	0.116	0.84 (0.66–1.08)	0.175	0.85 (0.63–1.14)	0.272
Phenyl sulfate (Q4 vs. Q1)	0.60 (0.33–1.08)	0.086	0.64 (0.35–1.17)	0.145	0.45 (0.19–1.05)	0.065

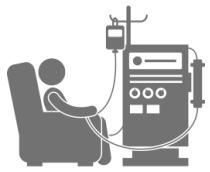


HD (*n* = 329)

Hung SC et al. 2025

Plasma Metabolites and Risk of Mortality in HD Patients

	Crude		Model 1		Model 2	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Tryptophan*	0.36 (0.18–0.72)	0.004	0.41 (0.21–0.80)	0.009	0.28 (0.09–0.89)	0.030.
Tryptophan (Q4 vs. Q1)	0.51 (0.29–0.90)	0.020	0.53 (0.30–0.94)	0.031	0.61 (0.27–1.37)	0.234
Indole glucuronide*	1.08 (0.84–1.38)	0.570	1.25 (0.98–1.60)	0.078	1.48 (1.01–2.16)	0.042
Indole glucuronide (Q4 vs. Q1)	1.22 (0.67–2.24)	0.513	1.43 (0.76–2.70)	0.269	2.20 (0.88–5.46)	0.089
5-OH-indole-3-acetic acid*	**1.27 (0.77–2.08)**	**0.344**	**1.66 (0.99–2.77)**	**0.051**	**2.33 (1.13–4.80)**	**0.021**
5-OH-indole-3-acetic acid (Q4 vs. Q1)	**1.10 (0.62–1.96)**	**0.749**	**1.57 (0.84–2.93)**	**0.160**	**2.73 (1.01–7.40)**	**0.048**
Indoxyl sulfate*	0.91 (0.69–1.21)	0.511	1.03 (0.74–1.43)	0.855	1.85 (0.96–3.55)	0.065
Indoxyl sulfate (Q4 vs. Q1)	1.04 (0.61–1.79)	0.877	1.33 (0.75–2.35)	0.331	1.83 (0.69–4.86)	0.223
Indole-3-lactic acid*	**0.47 (0.31–0.72)**	**<0.001**	**0.60 (0.39–0.91)**	**0.017**	**0.46 (0.25–0.84)**	**0.012**
Indole-3-lactic acid (Q4 vs. Q1)	**0.38 (0.20–0.71)**	**0.003**	**0.47 (0.25–0.89)**	**0.020**	**0.45 (0.20–0.98)**	**0.044**
N-Acetyl-Tryptophan*	0.84 (0.57–1.25)	0.387	1.02 (0.69–1.52)	0.909	0.82 (0.47–1.42)	0.470
N-Acetyl-Tryptophan (Q4 vs. Q1)	0.74 (0.43–1.28)	0.282	0.97 (0.54–1.72)	0.906	1.48 (0.62–3.54)	0.373
Serotonin*	1.06 (0.85–1.32)	0.604	1.04 (0.83–1.31)	0.728	1.11 (0.86–1.44)	0.423
Serotonin (Q4 vs. Q1)	1.24 (0.57–2.68)	0.586	1.42 (0.64–3.13)	0.389	1.25 (0.43–3.65)	0.679
Indole-3-acetic acid*	0.67 (0.46–0.96)	0.029	0.70 (0.49–0.99)	0.045	0.89 (0.57–1.38)	0.595
Indole-3-acetic acid (Q4 vs. Q1)	0.58 (0.32–1.06)	0.075	0.59 (0.32–1.08)	0.088	0.93 (0.42–2.05)	0.860
Indole-3-propionic acid*	0.89 (0.73–1.08)	0.224	0.93 (0.76–1.14)	0.497	0.88 (0.70–1.11)	0.268
Indole-3-propionic acid (Q4 vs. Q1)	0.65 (0.36–1.18)	0.158	0.73 (0.40–1.34)	0.311	0.71 (0.33–1.55)	0.387



HD (*n* = 329)

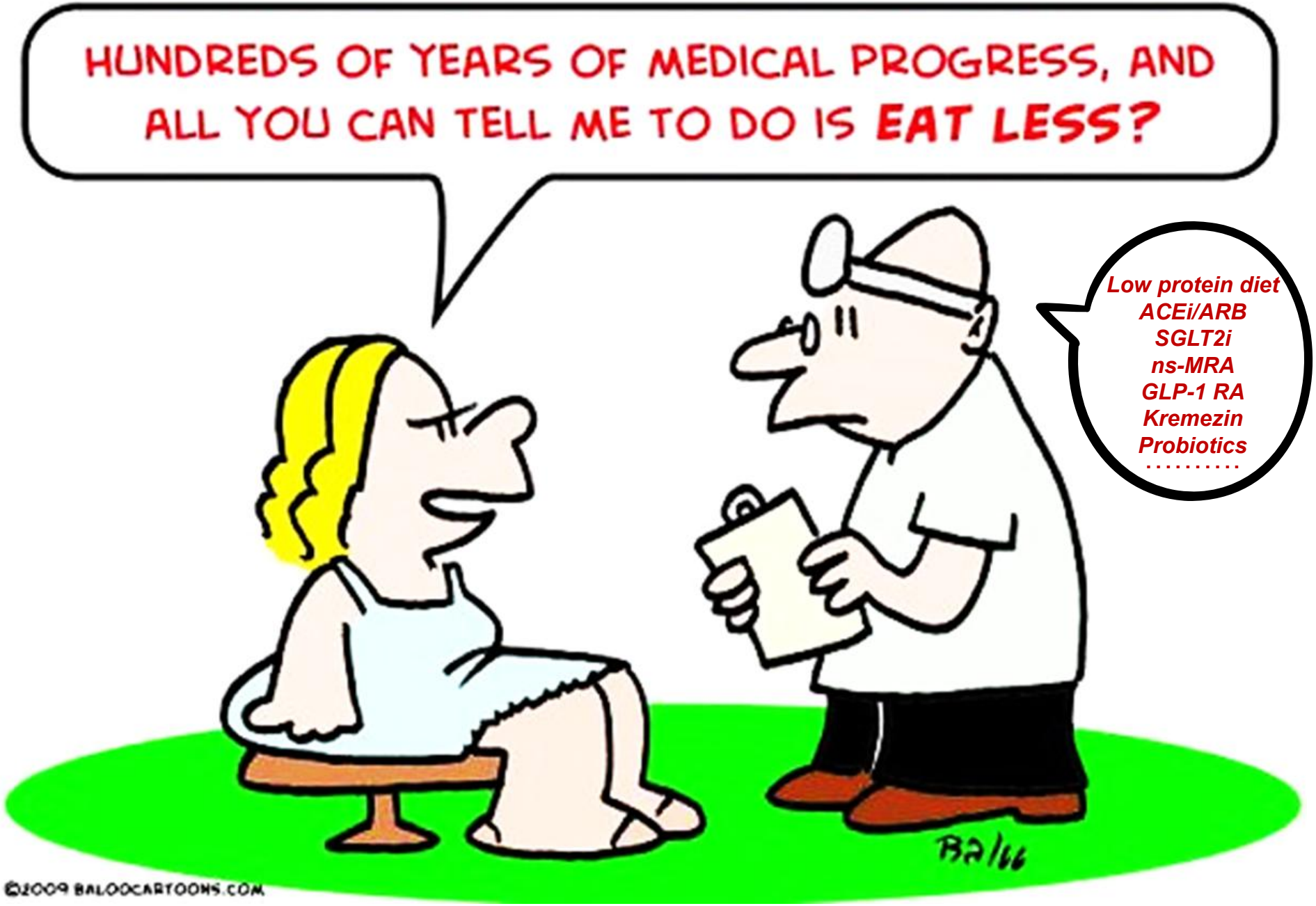
Hung SC et al. 2025

Take Home Message

- Micronutrient deficiencies are common and clinically important, yet they're often overlooked.
- The BMI paradox in CKD actually reflects the confounding of underlying nutritional status, highlighting the need for more precise assessments of body composition to guide clinical care.
- CKD-related wasting, particularly in patients with normal BMI, is often inflammation-driven. Simply adding calories or protein does not correct this type 2 malnutrition.
- Effective care requires addressing the underlying inflammatory drivers, such as GDF-15 and gut dysbiosis.

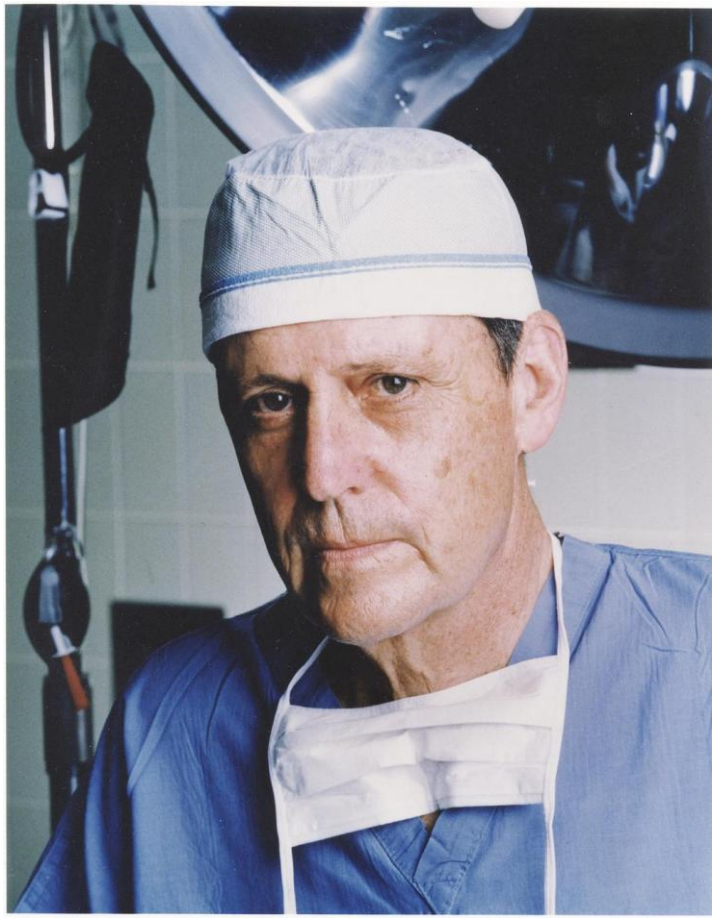
Take Home Message

- Instead of focusing solely on grams of protein, we must consider the source. Plant-based diets reduce TMAO and lower the risk of CKM syndrome, while supporting nutritional adequacy with no increased risk of hyperkalemia.
- Patients differ in their gut microbiome, metabolic responses, and toxin production. Universal recommendations of a low-protein diet for CKD patients have limited utility.
- Oral amino acid challenge test is a step toward identifying at-risk patients. Modulating the gut microbiota through diet or probiotics could reduce toxin burden, moving us beyond simple restriction.


HUNDREDS OF YEARS OF MEDICAL PROGRESS, AND ALL YOU CAN TELL ME TO DO IS EAT LESS?
Low protein diet
ACEi/ARB
SGLT2i
ns-MRA
GLP-1 RA
Kremezin
Probiotics
.....
©2009 BALOOCARTOONS.COM

Precision Nutrition in CKD

Is It Time?



Thomas Starzl (1926-2017)

"The history of medicine is that what was inconceivable yesterday, and barely achievable today, often becomes routine tomorrow."

Der-Cherng Tarng

Shuei-Liong Lin

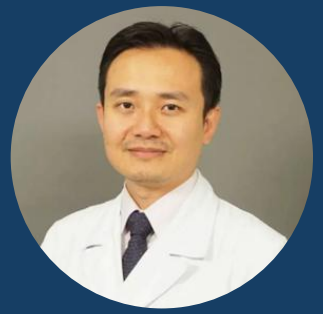
Paik-Seong Lim

Shih-Hua Lin

Ting-Yun Lin

Fang-Chi Chang

Huang-Yu Yang



Yen-Ling Chiu

Chien-Yu Lin

Ping-Hsun Wu