December 5, 2025
ACPN x TSN 2025
Symposium: “Gut Microbiome and Metabolomics in CKD”
Prof. Takaaki Abe, Prof. I-Wen Wu

Uremic toxins and systemic complications in patients with kidney disease

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APCN x TSN 2025 Disclosure

Suguru Yamamoto

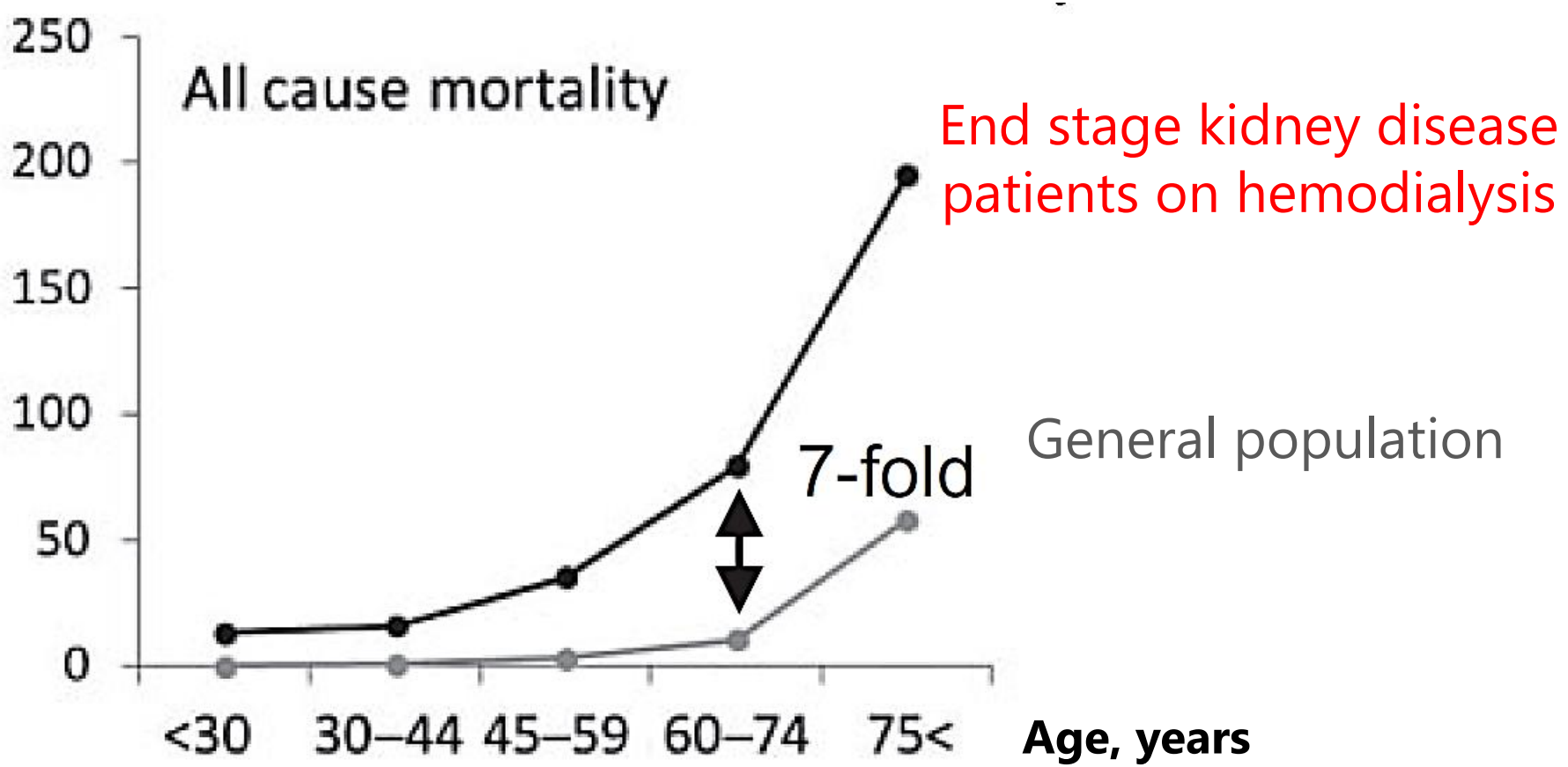
Lecture Fees:

Ono Pharmaceutical Co., Ltd., Kaneka Corporation, Kissei Pharmaceutical Co., Ltd., Kyowa Kirin Co., Ltd., Ono Pharmaceutical Co., Ltd., Sanwa Kagaku Kenkyusho Co., Ltd., Fuso Pharmaceutical Industries, Ltd.

Commissioned Research / Collaborative Research Funding:

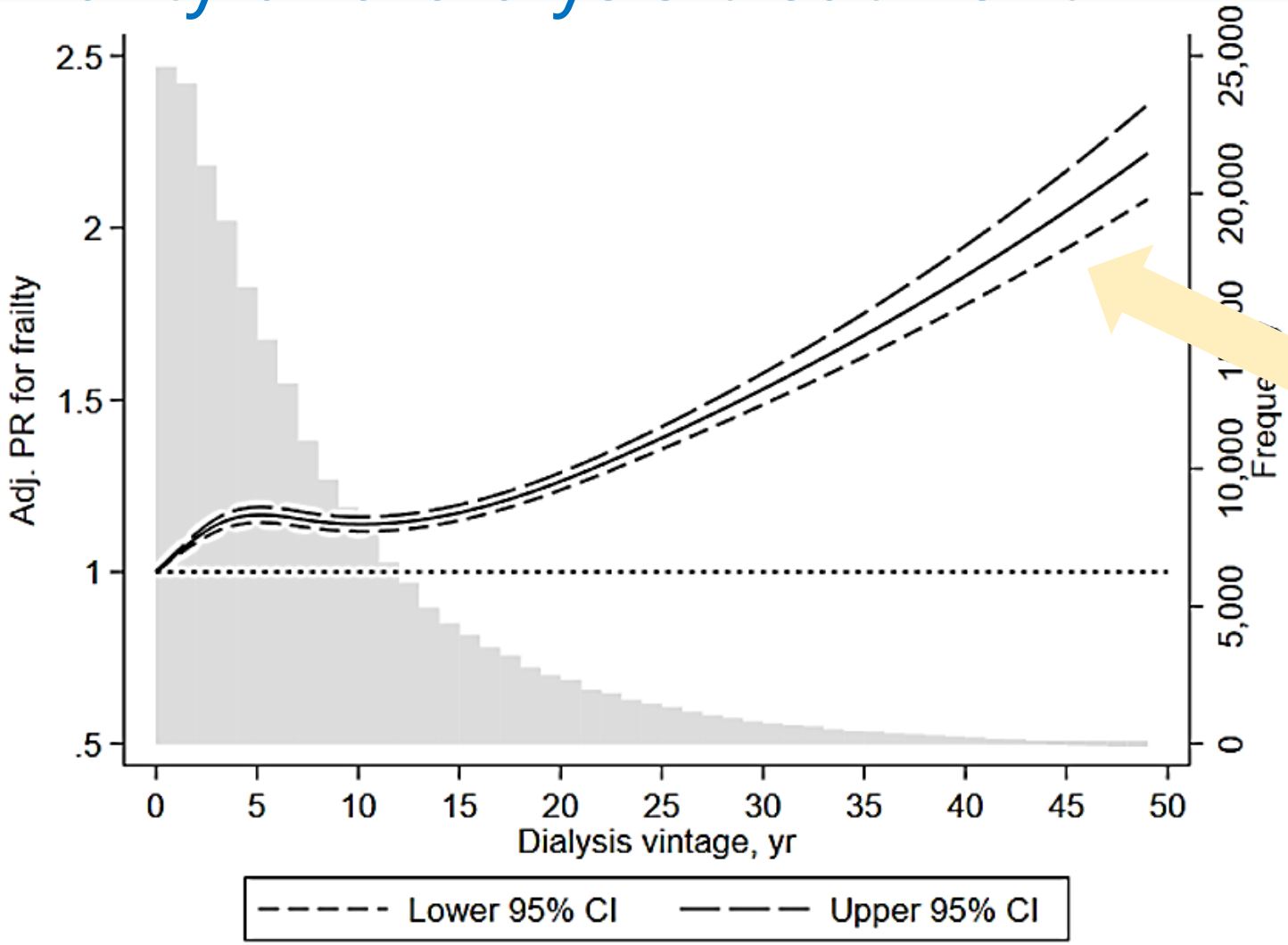
Toagosei Co., Ltd., Kaneka Corporation, Kureha Corporation, Kyowa Kirin Co., Ltd., Toray Medical Co., Ltd.

Mortality in end-stage kidney disease patients



Wakasugi M, Yamamoto S, Ther Apher Dial, 2013

Frailty and dialysis treatment



Unresolved and/or unrecognized pathophysiology

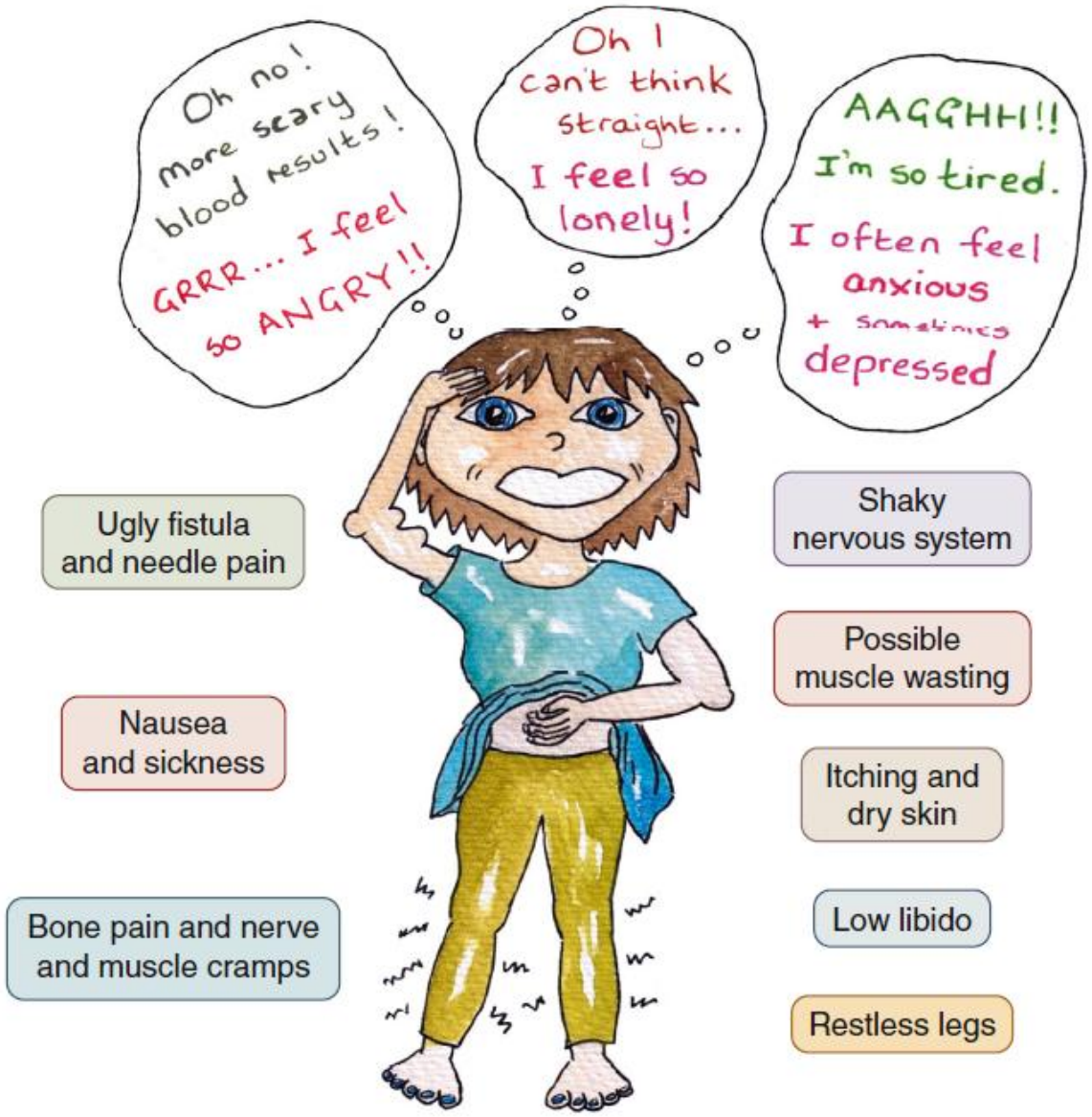
Adjusted for age, sex, corrected calcium, phosphorus, parathyroid hormone, β2MG, creatinine index, albumin, diabetes, dementia, ischemic heart disease, cerebral hemorrhage, cerebral infarction, limb amputation, carpal tunnel syndrome, hip fracture, and vascular access type.

Yamamoto S, Am J Kidney Dis, 2024

Managing the symptom burden associated with maintenance dialysis: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

Rajnish Mehrotra[1], Sara N. Davison[2], Ken Farrington[3], Jennifer E. Flythe[4,5], Marjc
Magdalena Madero[7], Rachael L. Morton[8], Yusuke Tsukamoto[9], Mark L. Unruh[10],
Michel Jadoul[12], Wolfgang C. Winkelmayer[13] and Edwina A. Brown[14]; for Confe

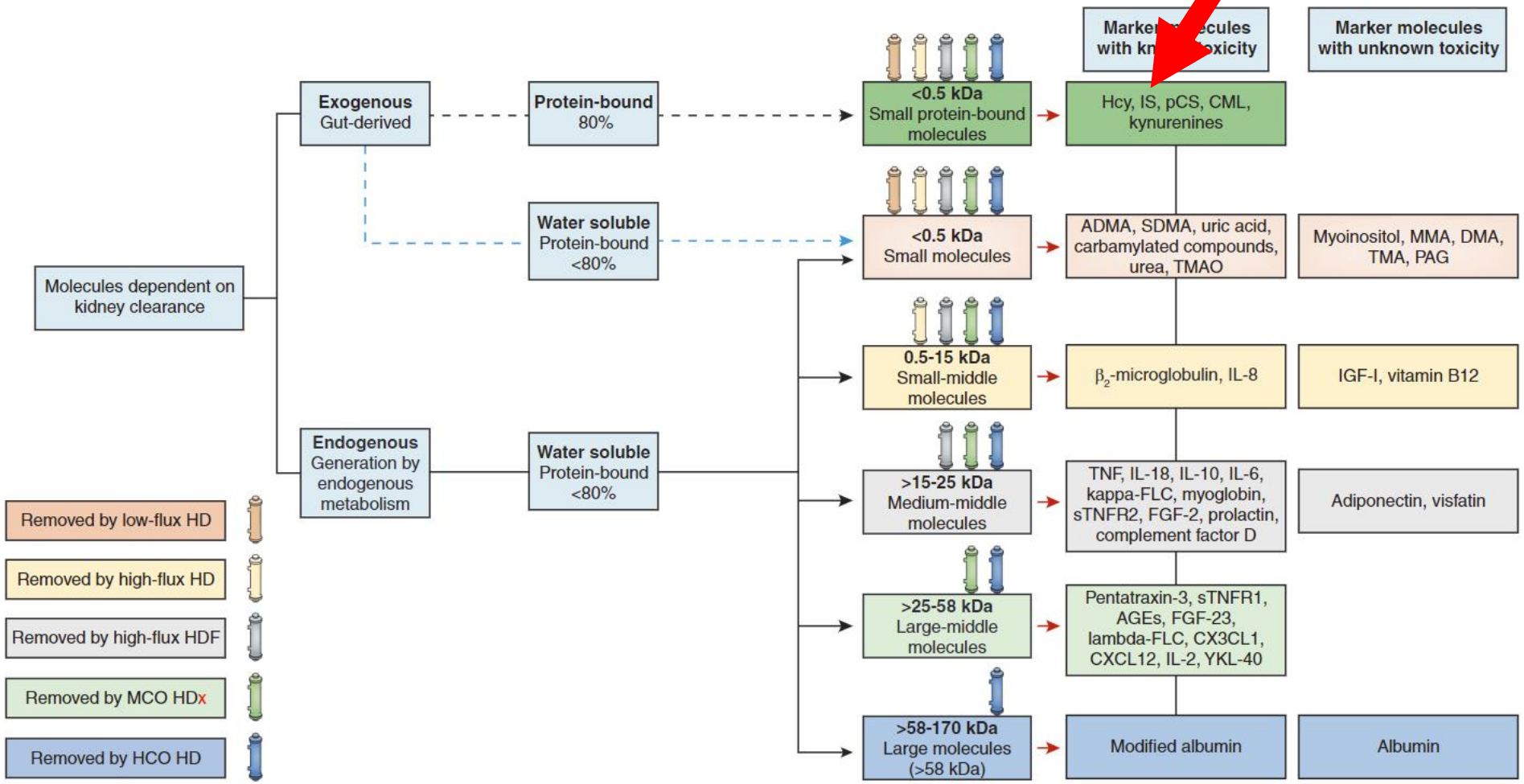
Uremic toxins



Mehrotra R, Kidney Int, 2023

Classification of uremic toxins

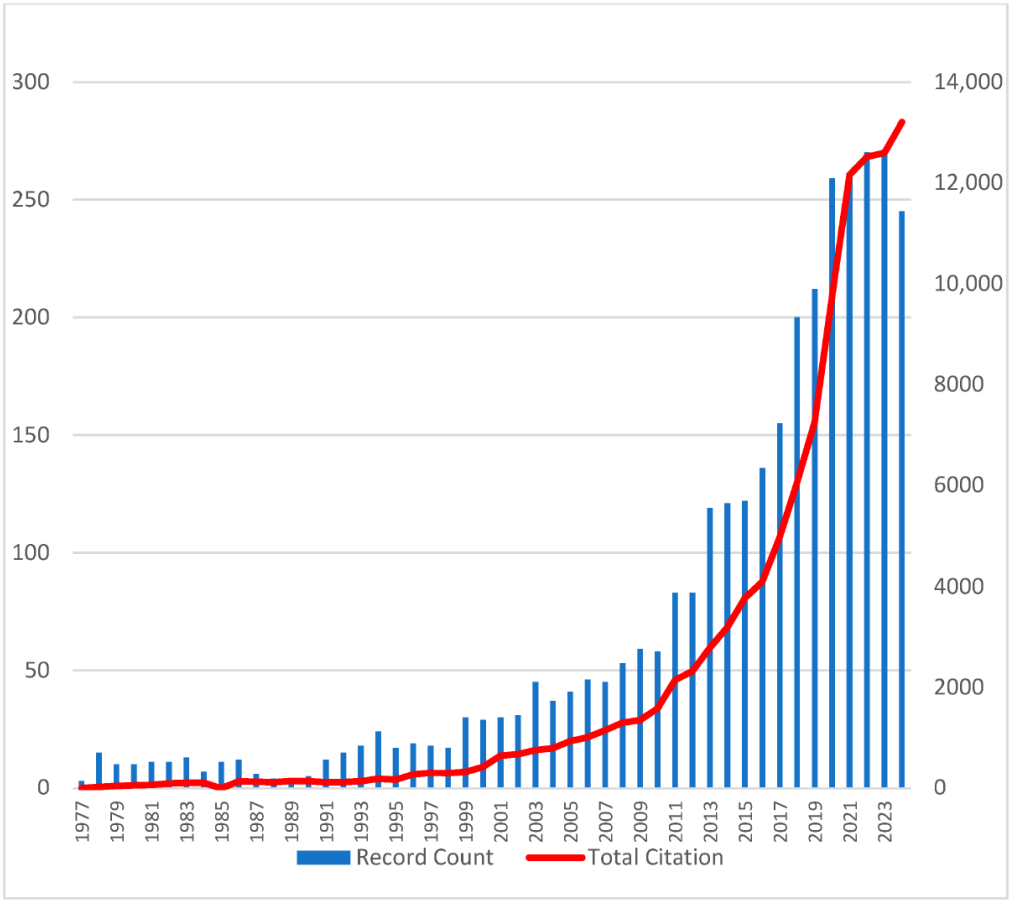
Small protein-bound molecules (SPBMs)



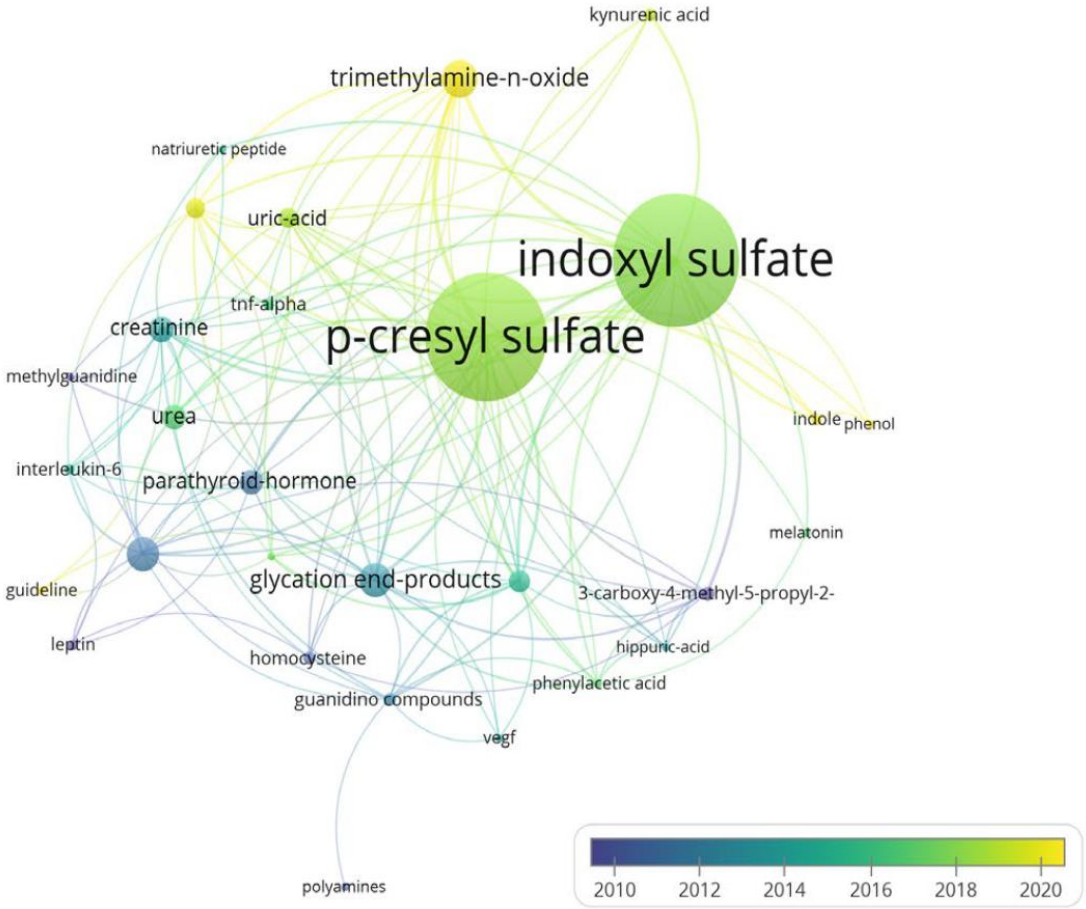
Rosner M. H. Clin J Am Soc Nephrol. 2021

Trends of uremic toxin research

Publication and citation



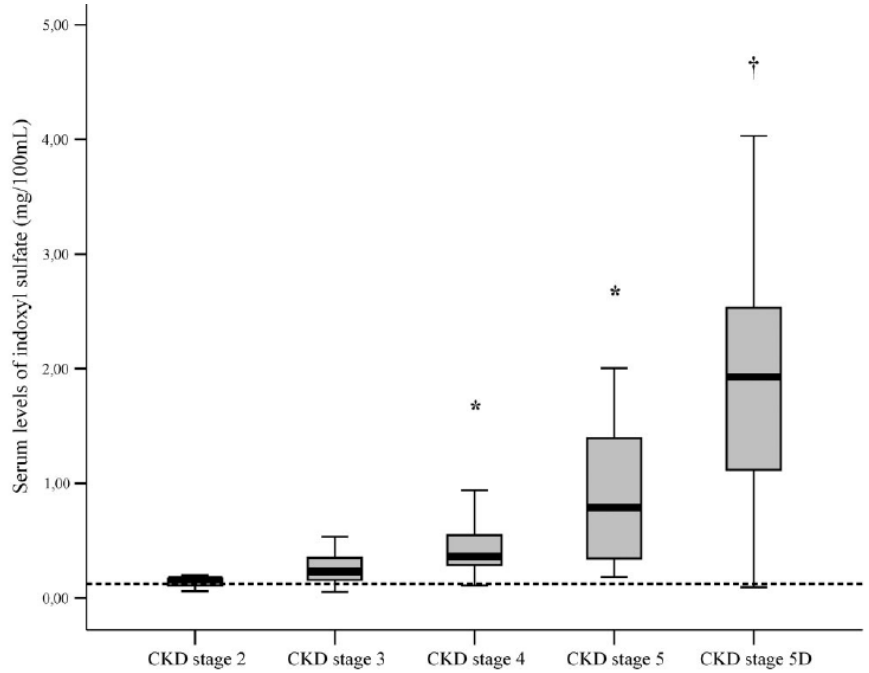
Topics of uremic toxin



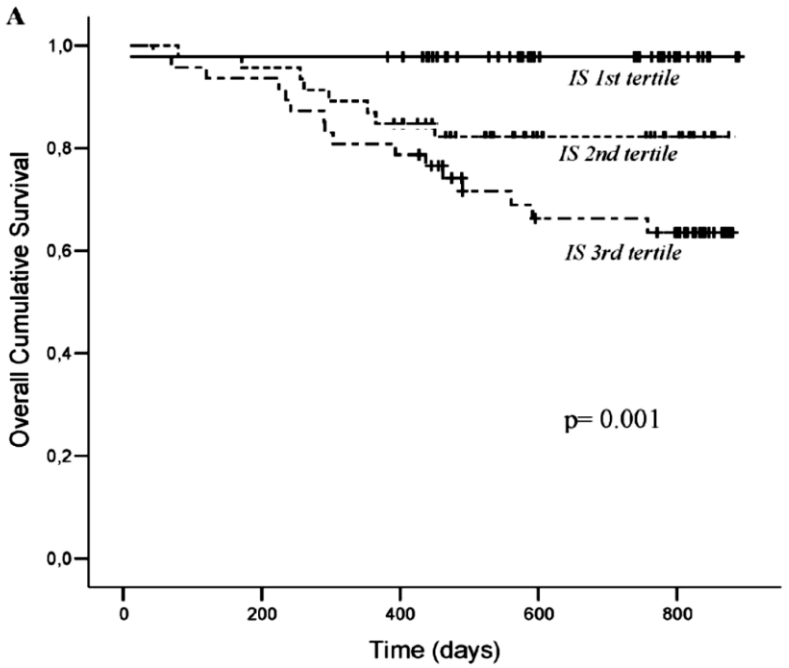
Hardjo M, Yamamoto S, Toxins, in press

Indoxyl sulfate and mortality in CKD 2-5D

Serum level of indoxyl sulfate

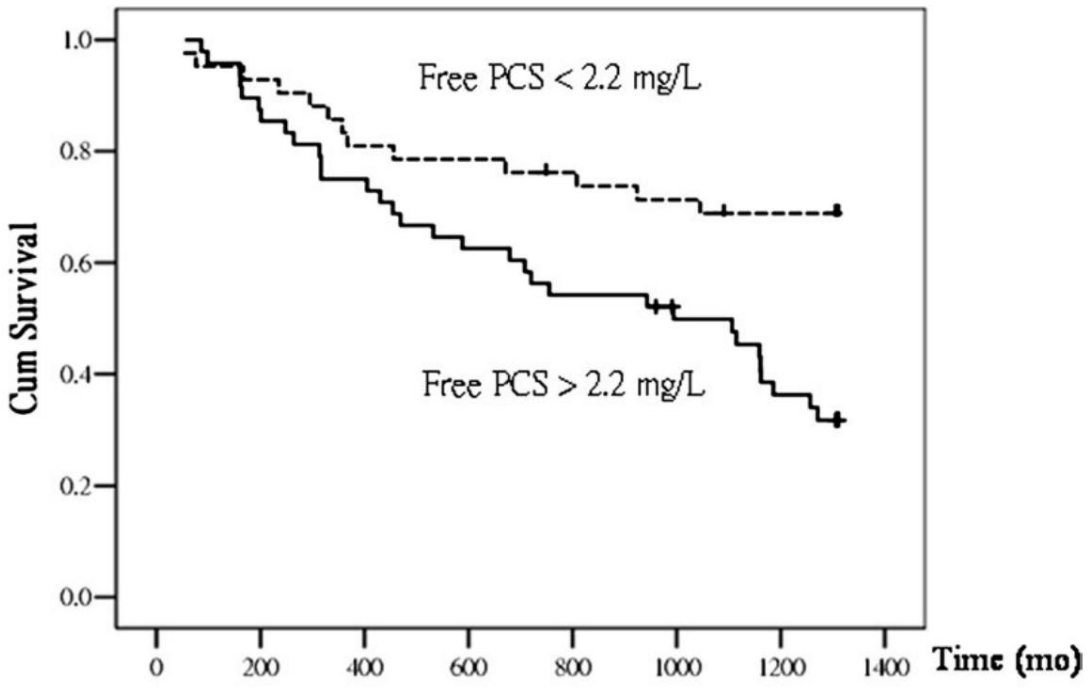


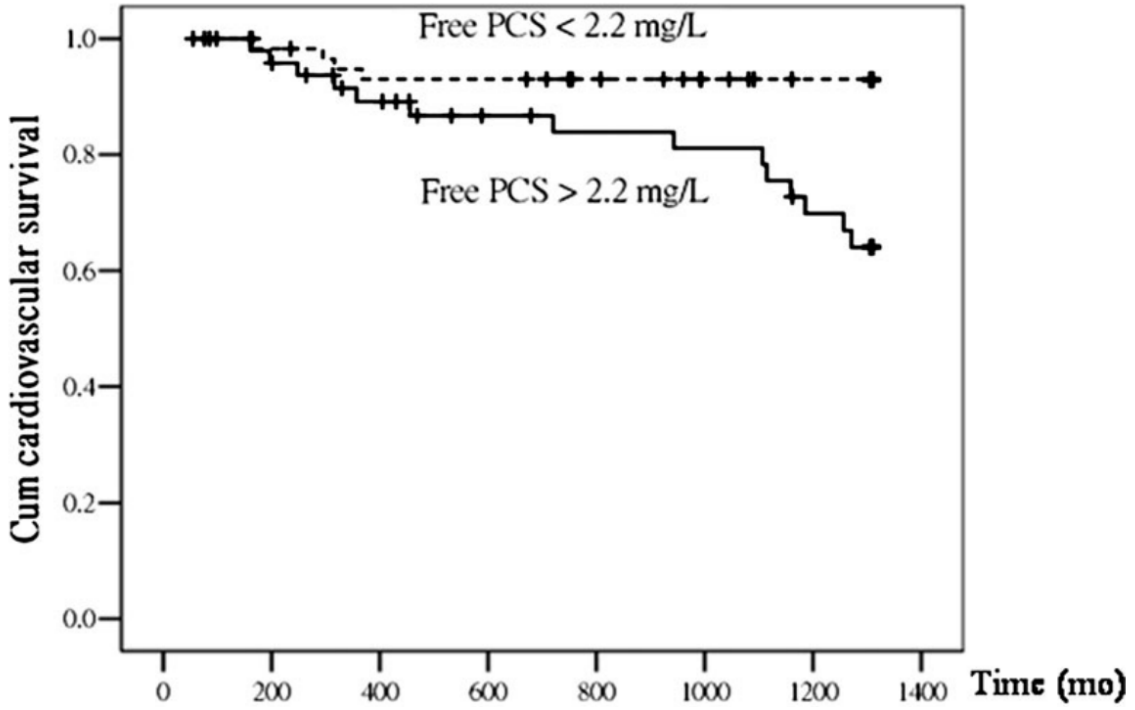
Indoxyl sulfate and mortality



Barreto FC. Clin J Am Soc Nephrol 2009

p-Cresyl sulfate and mortality in patients with hemodialysis





Wu I, Nephrol Dial Transplant 2012

Indoxyl sulfate and clinical outcomes in patients undergoing hemodialysis

JDOPPS
Dialysis Outcomes and Practice Patterns Study in Japan

Study Population:
1,170 Japanese hemodialysis patients (2012–2015)

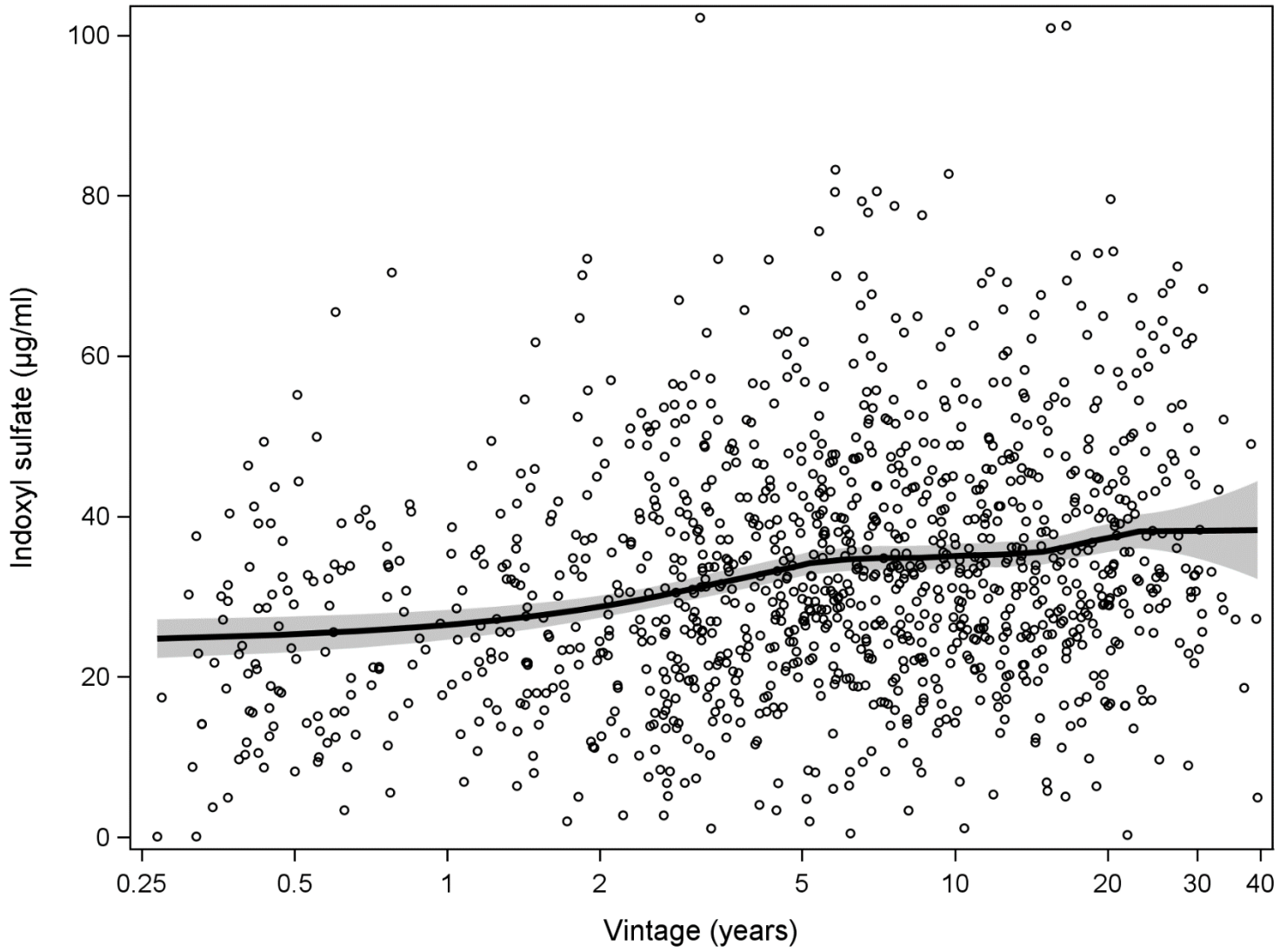
Exposure:
Baseline serum IS levels measured by HPLC

Outcomes:
All-cause mortality
Cardiovascular events (death + hospitalization)
Infectious disease events (death + hospitalization)

Analysis:
Cox regression analysis: From serum sampling to 2015
Adjustment Factors: Age, sex, dialysis vintage, diabetes, history of cardiovascular disease, albumin, nPCR, BMI, creatinine, spKt/V

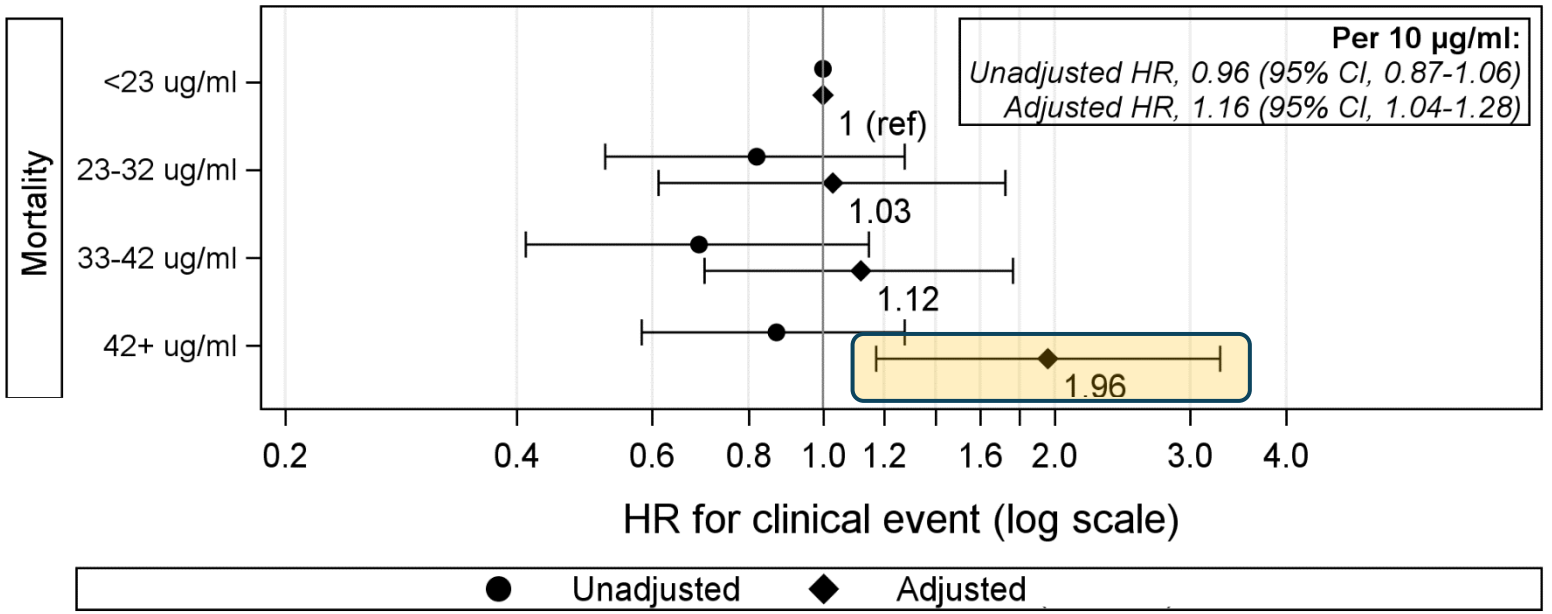
Yamamoto S, Clin Kidney J 2020

Serum indoxyl sulfate level with dialysis vintage



Yamamoto S, Clin Kidney J 2020

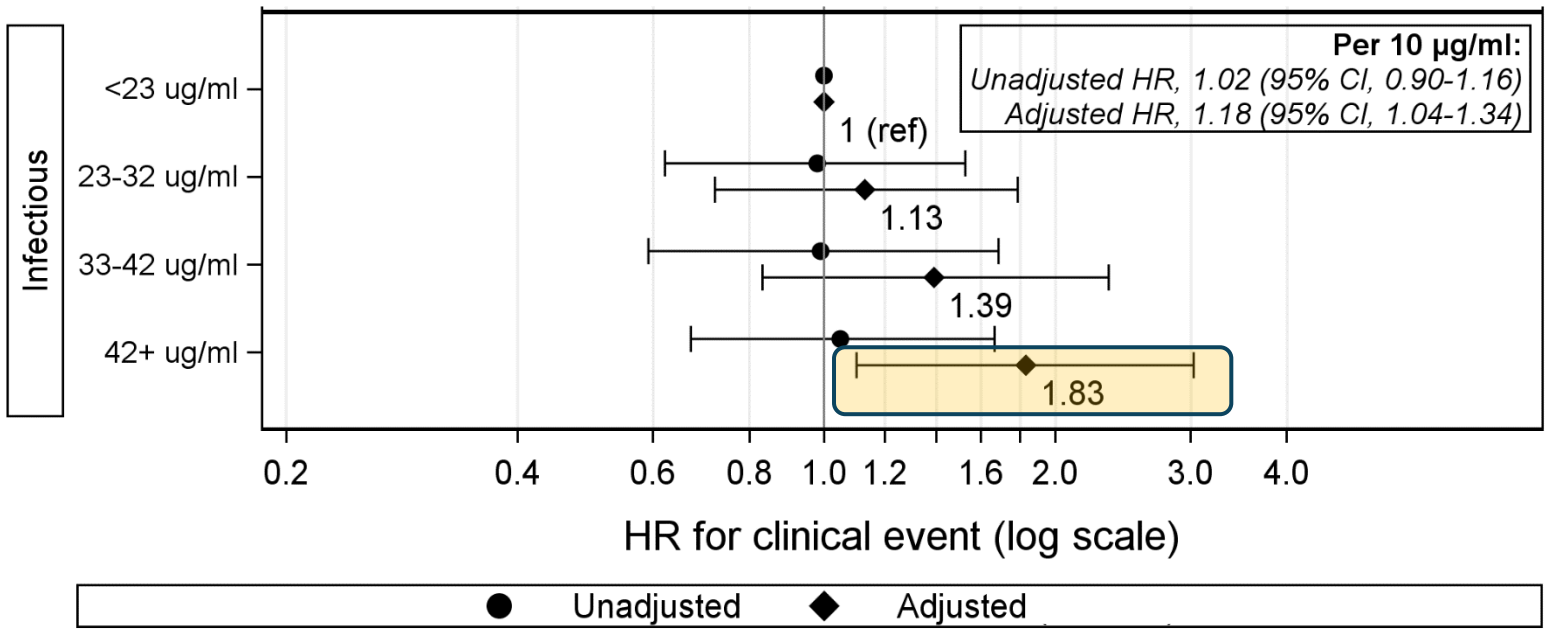
Serum indoxyl sulfate level and all-cause mortality



"Adjusted" model includes age, sex, vintage, history of diabetes, prior cardiovascular disease, markers of nutritional status (albumin, normalized protein-creatinine ratio, body-mass index, creatinine), and single-pool Kt/V.

Yamamoto S, Clin Kidney J 2020

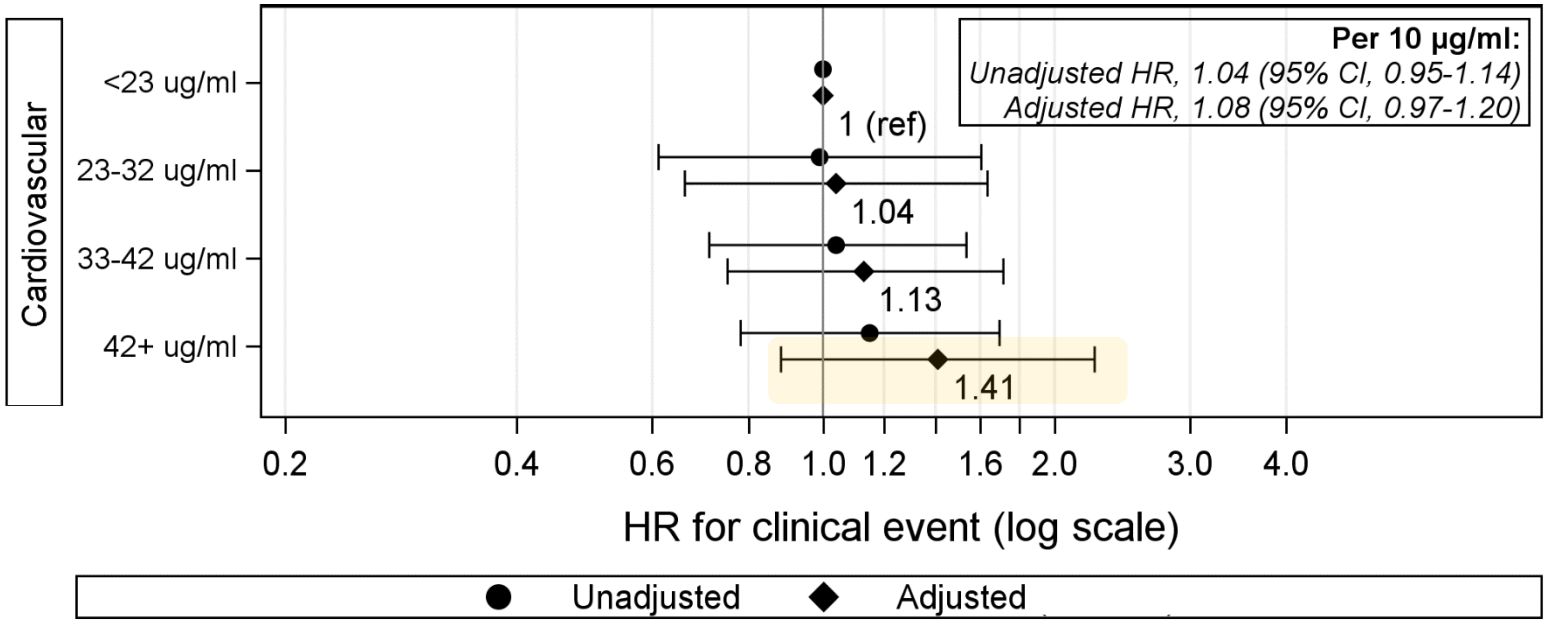
Serum indoxyl sulfate level and infectious events



"Adjusted" model includes age, sex, vintage, history of diabetes, prior cardiovascular disease, markers of nutritional status (albumin, normalized protein-creatinine ratio, body-mass index, creatinine), and single-pool Kt/V.

Yamamoto S. Clin Kidney J 2020

Serum indoxyl sulfate level and cardiovascular events



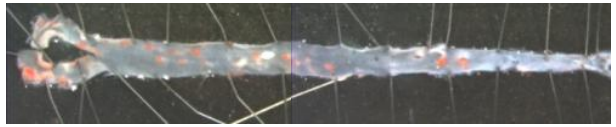
"Adjusted" model includes age, sex, vintage, history of diabetes, prior cardiovascular disease, markers of nutritional status (albumin, normalized protein-creatinine ratio, body-mass index, creatinine), and single-pool Kt/V.

Yamamoto S. Clin Kidney J 2020

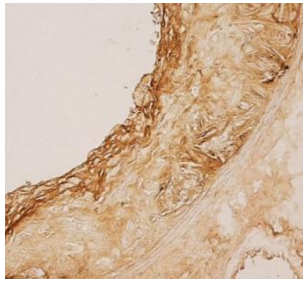
Accumulation of indoxyl sulfate in kidney injury-induced atherosclerosis

Normal kidney

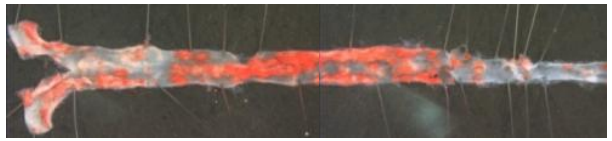
Sudan IV staining at 25 wks of age

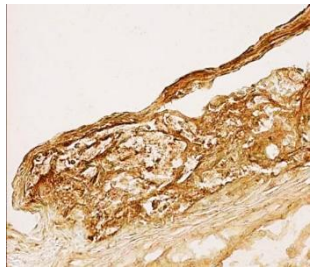


Indoxyl sulfate

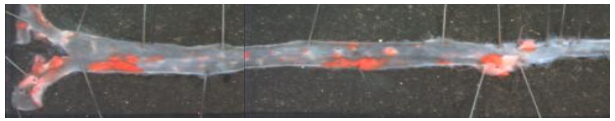


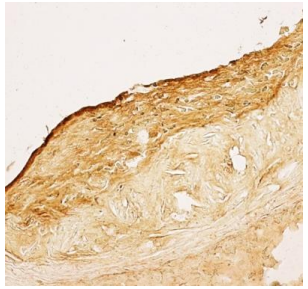
Subtotal nephrectomy at 8 wks of age





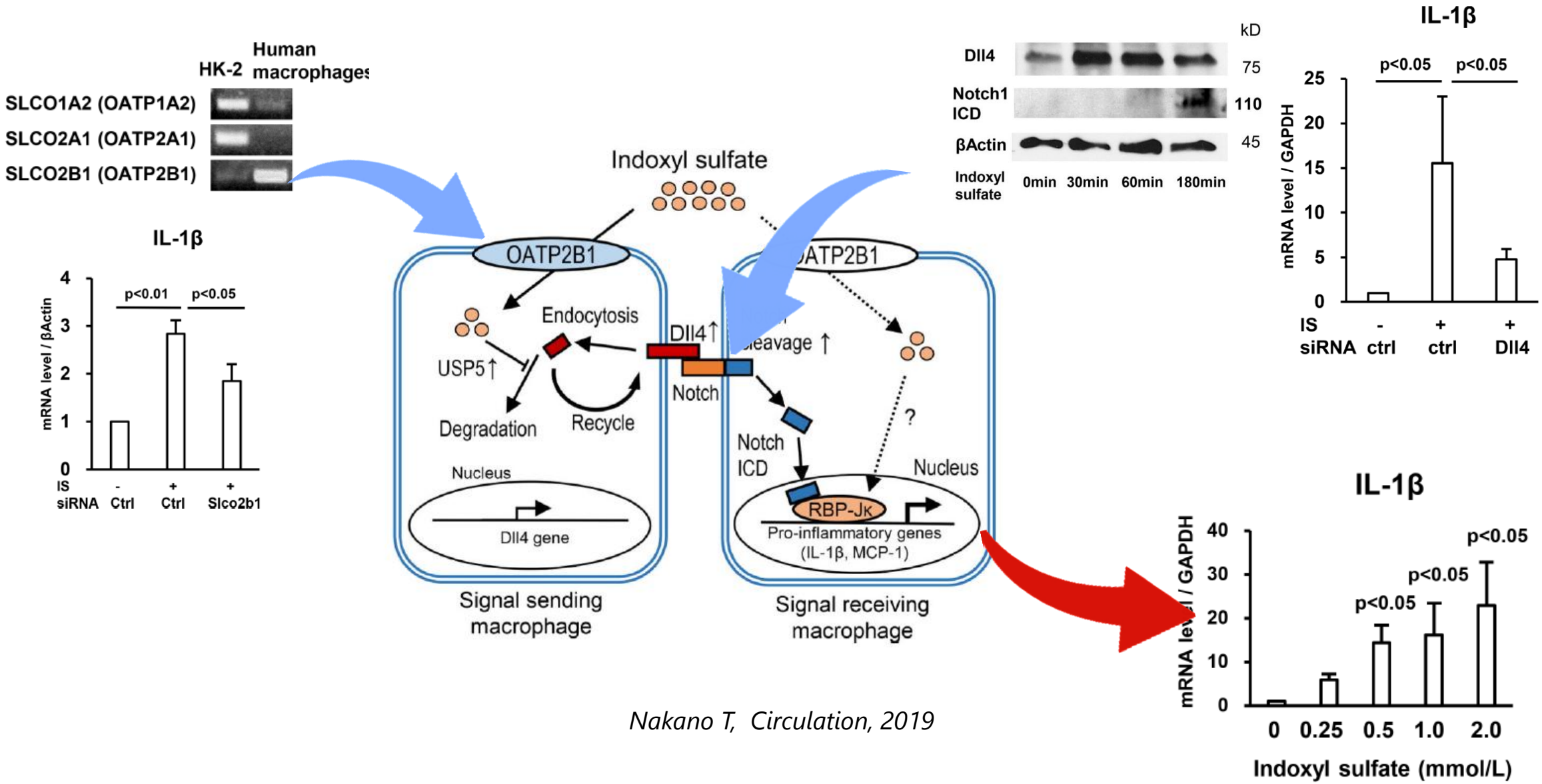
Subtotal nephrectomy and AST-120





Yamamoto S, Nephrol Dial Transplant 2011

Indoxyl sulfate induces macrophage inflammatory reaction



Nakano T, Circulation, 2019

The NEW ENGLAND JOURNAL of MEDICINE

IMAGES IN CLINICAL MEDICINE

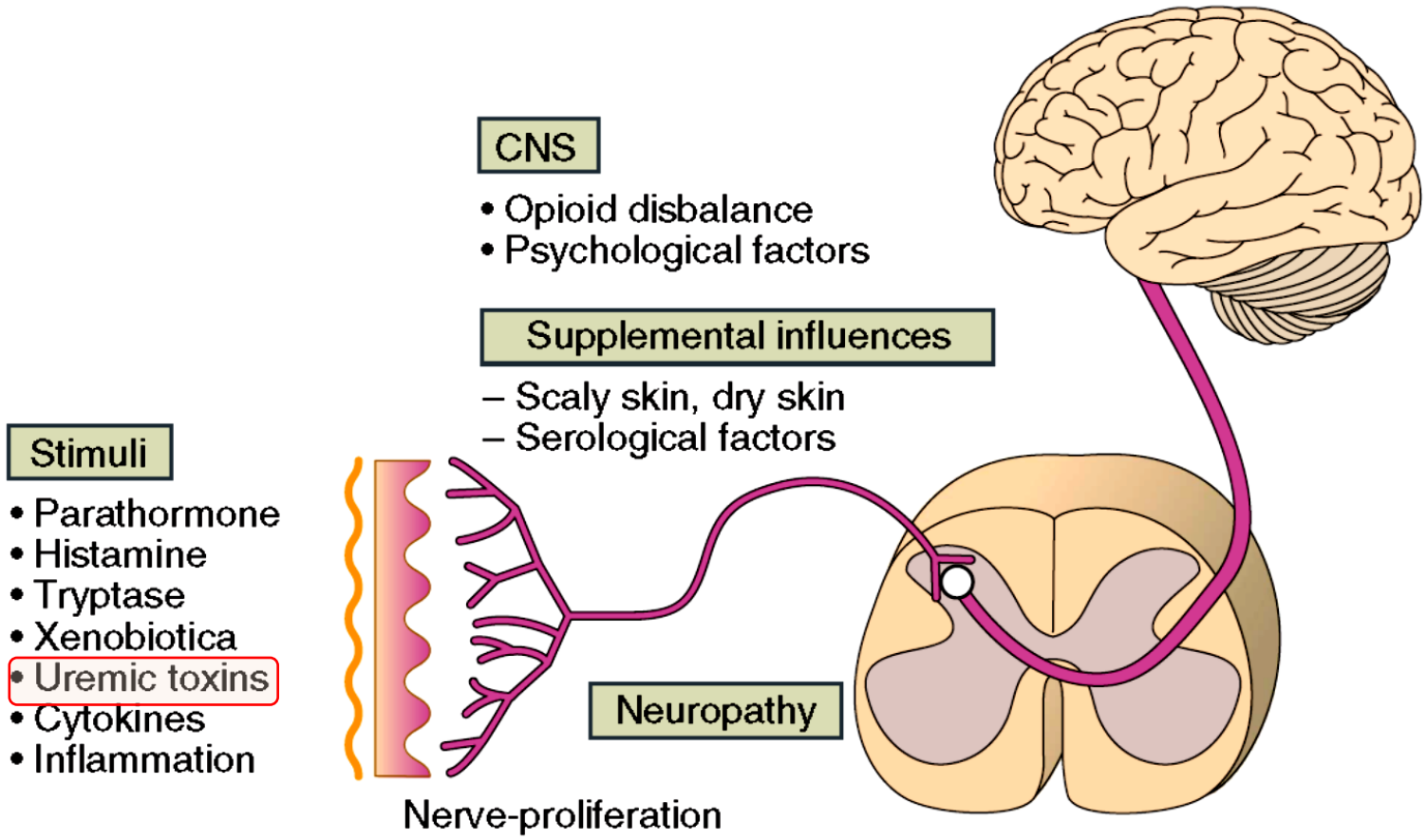
Stephanie V. Sherman, M.D., *Editor*

Chronic Generalized Pruritus

57 years-old man
Serum creatinine 15.2 mg/dL
Atrophic kidneys

Yokoyama T, N Eng J Med, 2022

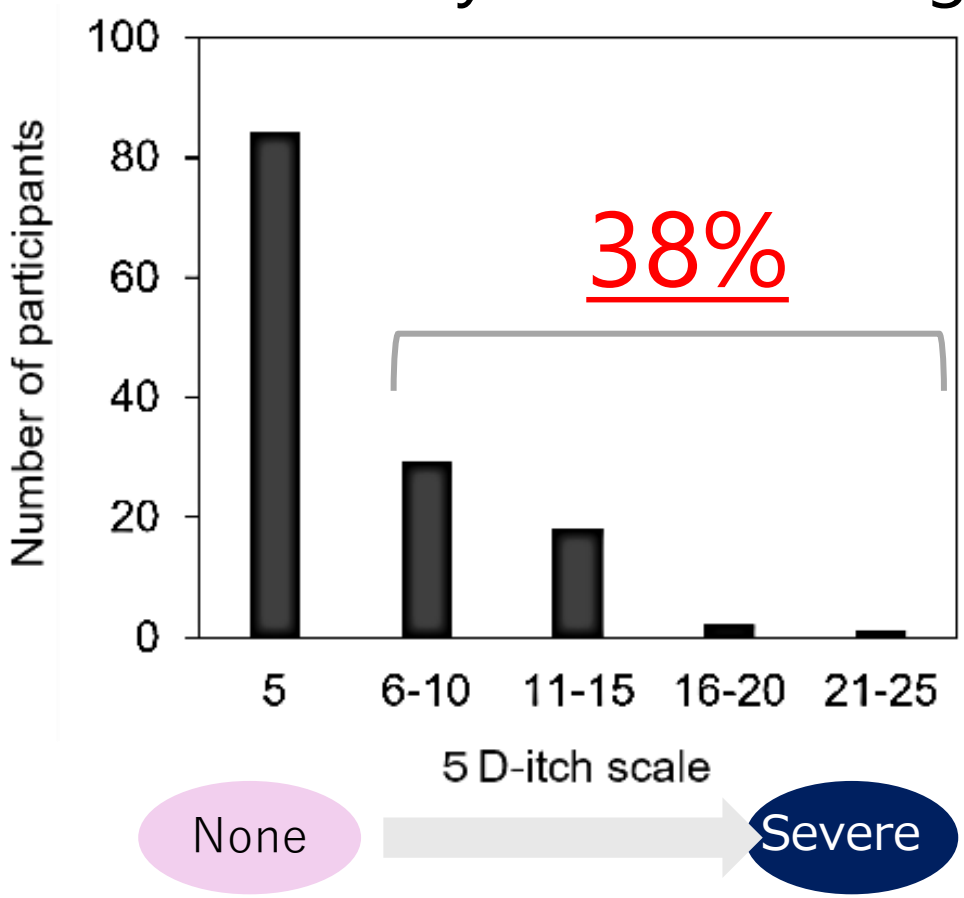
Mechanisms of uremic pruritus



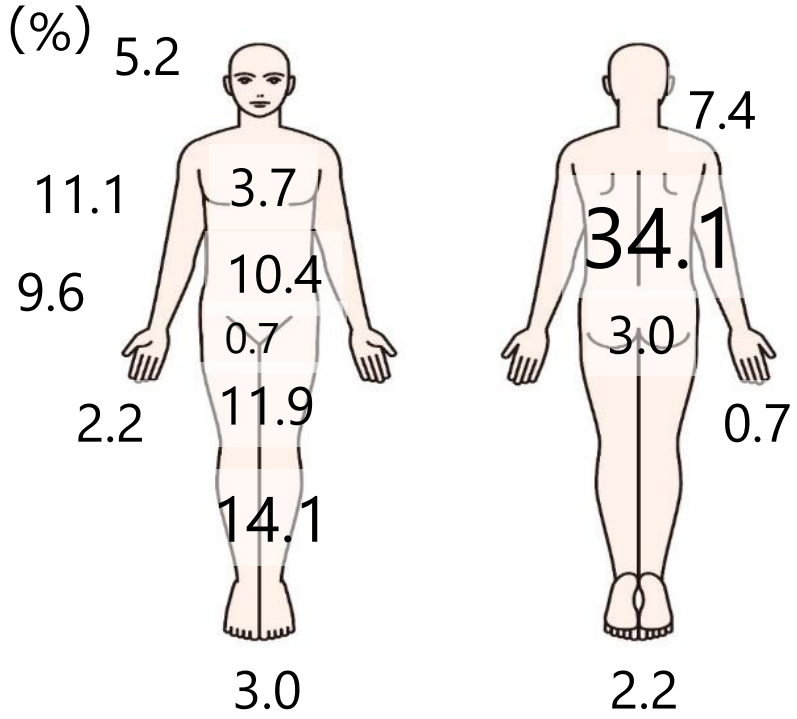
Mettang T, Kidney Int, 2015

Pruritus in hemodialysis patients

Severity of skin itching



Distribution of skin itching



Points of contact with clothing 2.2

Yamamoto S, Clin Kidney J, 2024

SPBM score with five molecules

	Coefficient (±SE)	OR (95% CI)	P value
Indoxyl sulfate, mg/dL	0.217±0.147	1.242 [0.931-1.658]	0.141
Phenyl sulfate, mg/dL	−0.0075±0.274	0.927 [0.542-1.586]	0.783
p-Cresyl sulfate, mg/dL	0.065±0.126	1.067 [0.833-1.367]	0.609
Hippuric acid, mg/dL	0.013±0.061	1.013 [0.899-1.142]	0.829
Indole acetic acid, mg/dL	0.389±2.228	1.476 [0.019-116.224]	0.861

Adjusted with age, gender, dialysis duration, and dialysis modality
SE: standard error, OR: odds ratio

Principal component analysis

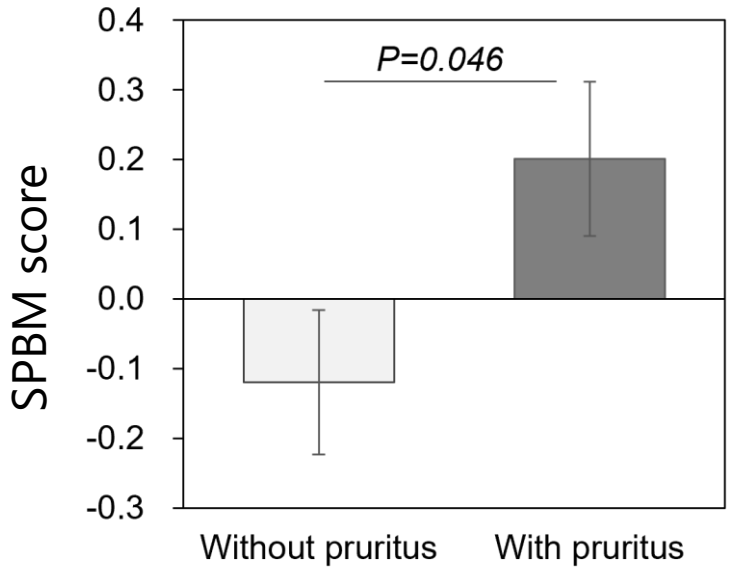
Variables	Factor score
Indoxyl sulfate	0.889
Phenyl sulfate	0.285
p-Cresyl sulfate	0.346
Hippuric acid	0.509
Indole acetic acid	-0.173

Eigenvalue: 1.821, Proportion (%): 36.4

SPBM score

Yamamoto S, Clin Kidney J, 2024

SPBM score and pruritus in hemodialysis patients

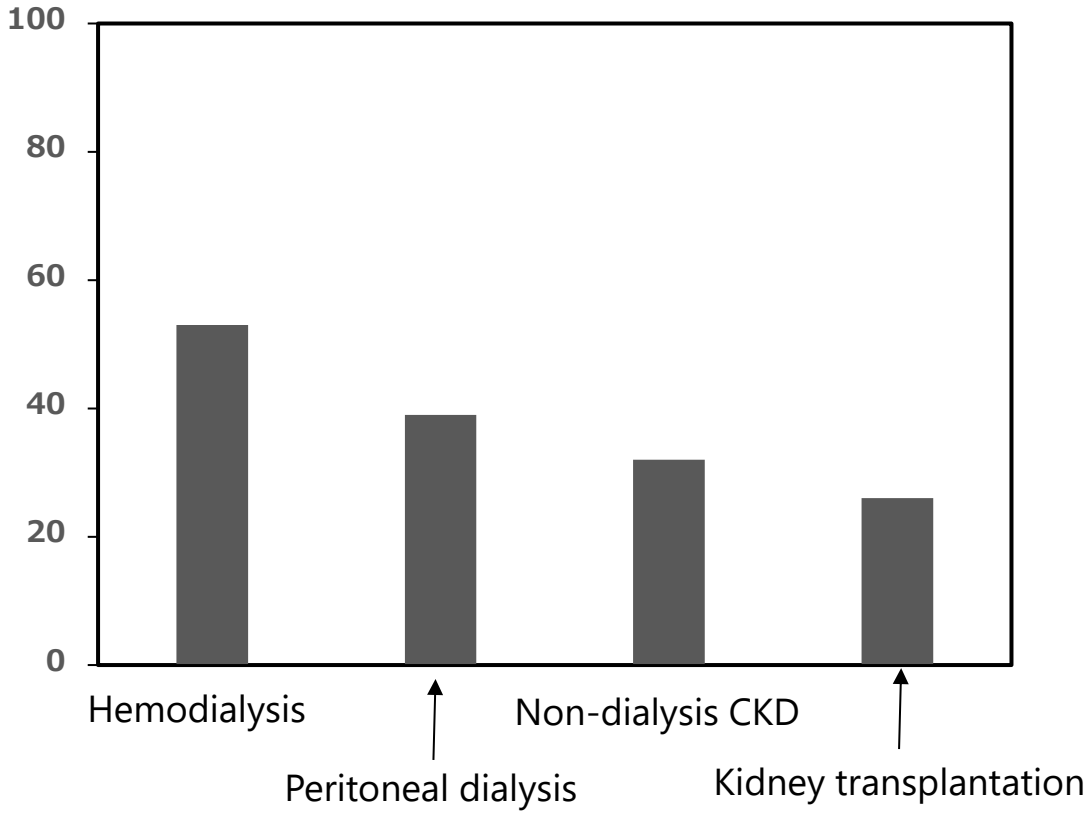


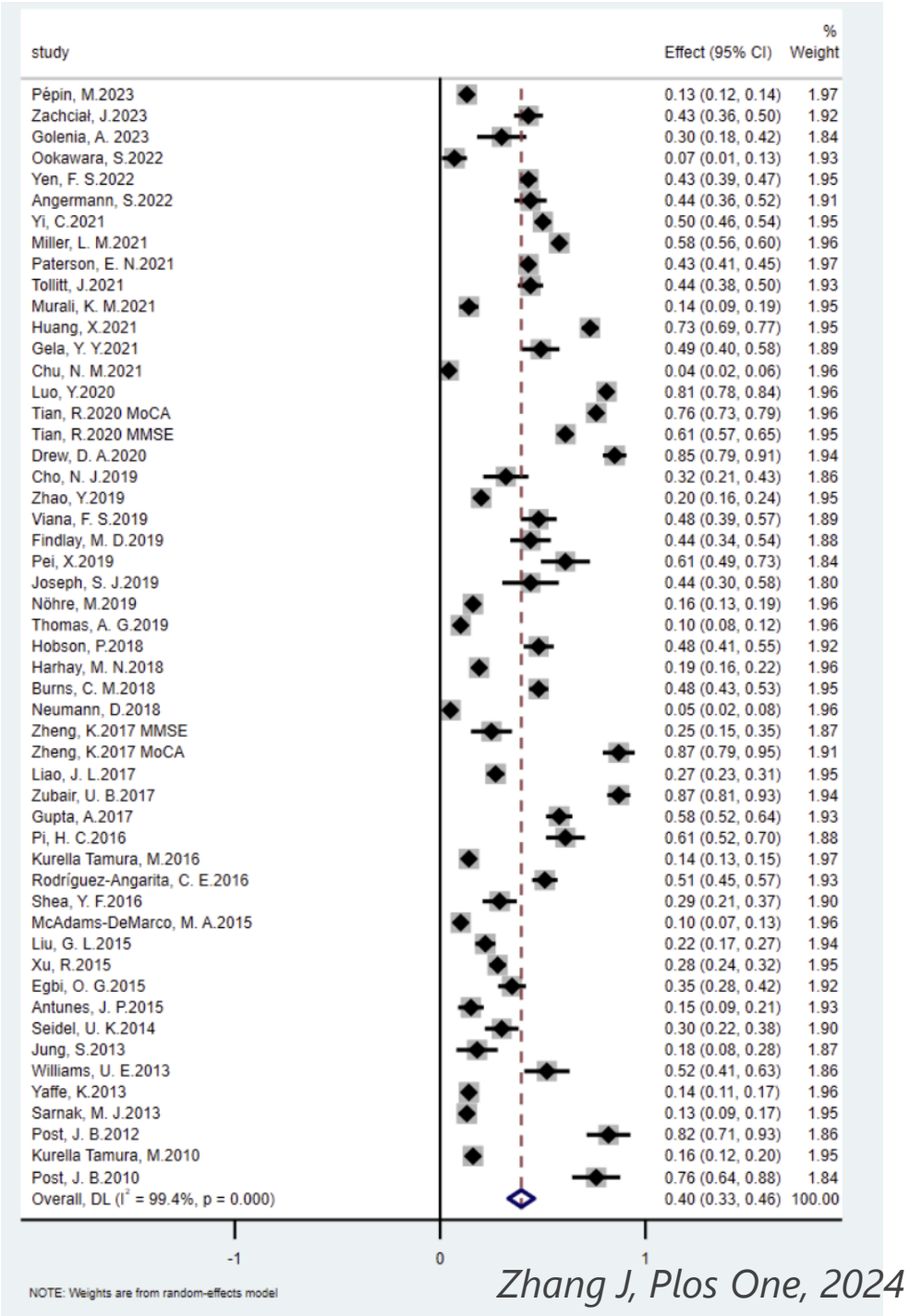
	Multivariate				
Independent variables	Coefficient	SE	Lower of 95% CI of coefficient	Upper of 95% CI of coefficient	P value
SPBM score	0.498	0.2251	0.057	0.939	0.027
Male sex	0.477	0.437	−0.38	1.333	0.275
Age >66 years old	−0.484	0.3813	−1.231	0.263	0.204
Dialysis modality (HDF)	1.622	0.4641	0.713	2.532	<0.001
Dialysis vintage	−0.485	0.2034	−0.884	−0.087	0.017
Kidney disease component summary	−0.023	0.0103	−0.043	−0.003	0.024

Yamamoto S, Clin Kidney J, 2024

CKD and cognitive impairment

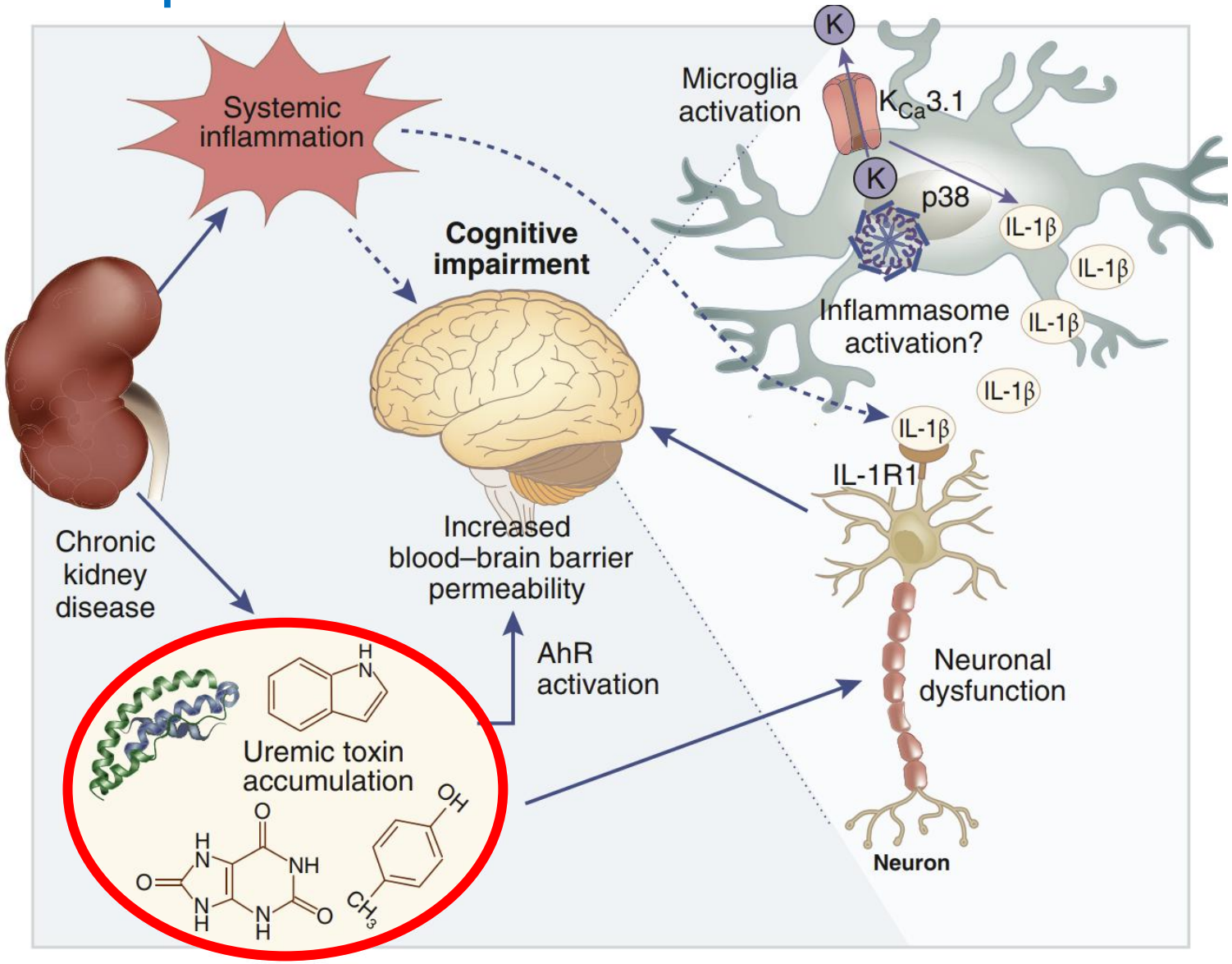
50 studies, 25,289 individuals with CKD
40% of them had cognitive impairment





Zhang J, Plos One, 2024

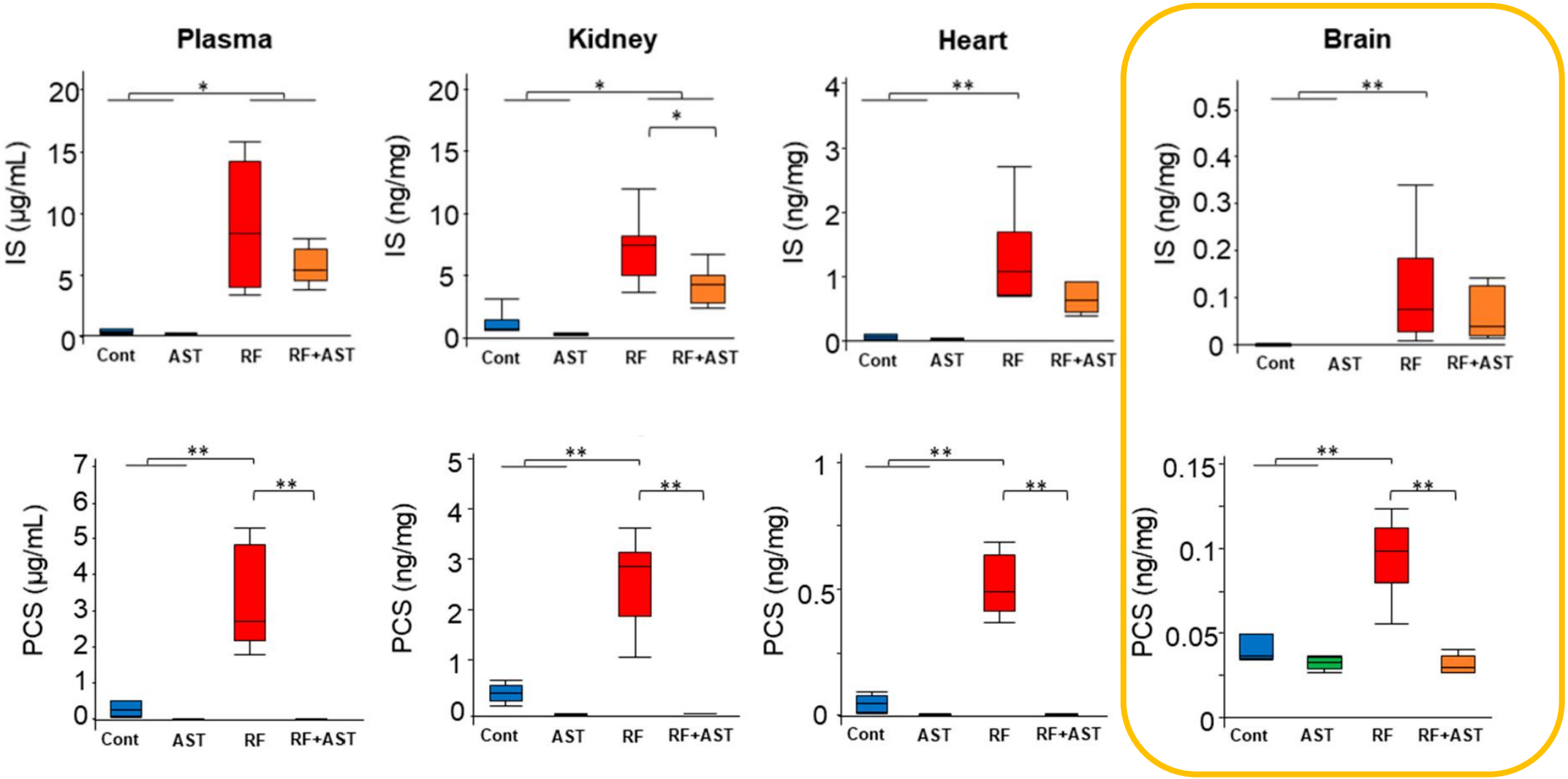
Cognitive impairment and SPBMs



Insufficient evidence in clinical studies

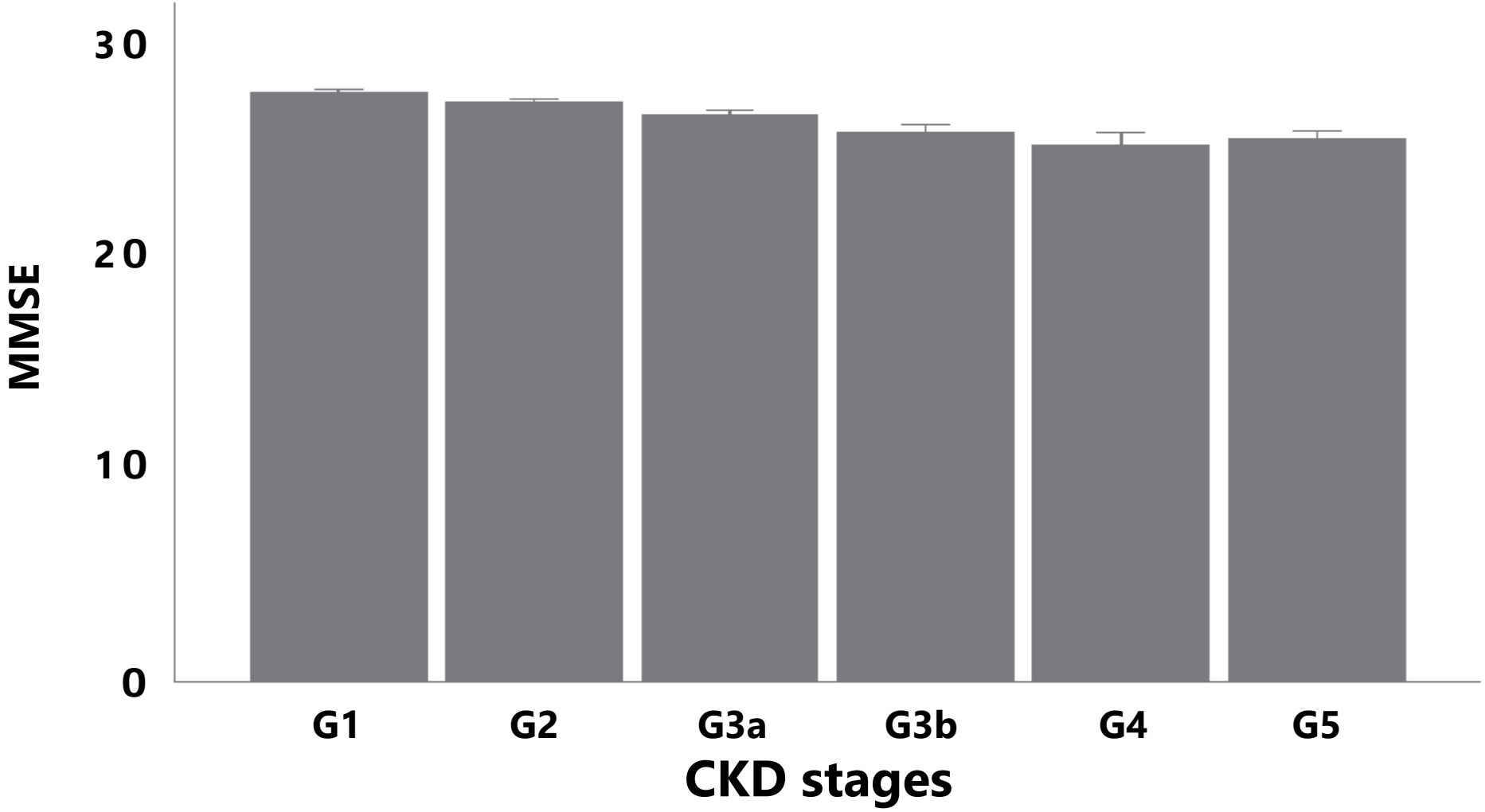
Bobot M, Kidney Int, 2024

SPBMs accumulate in the brain



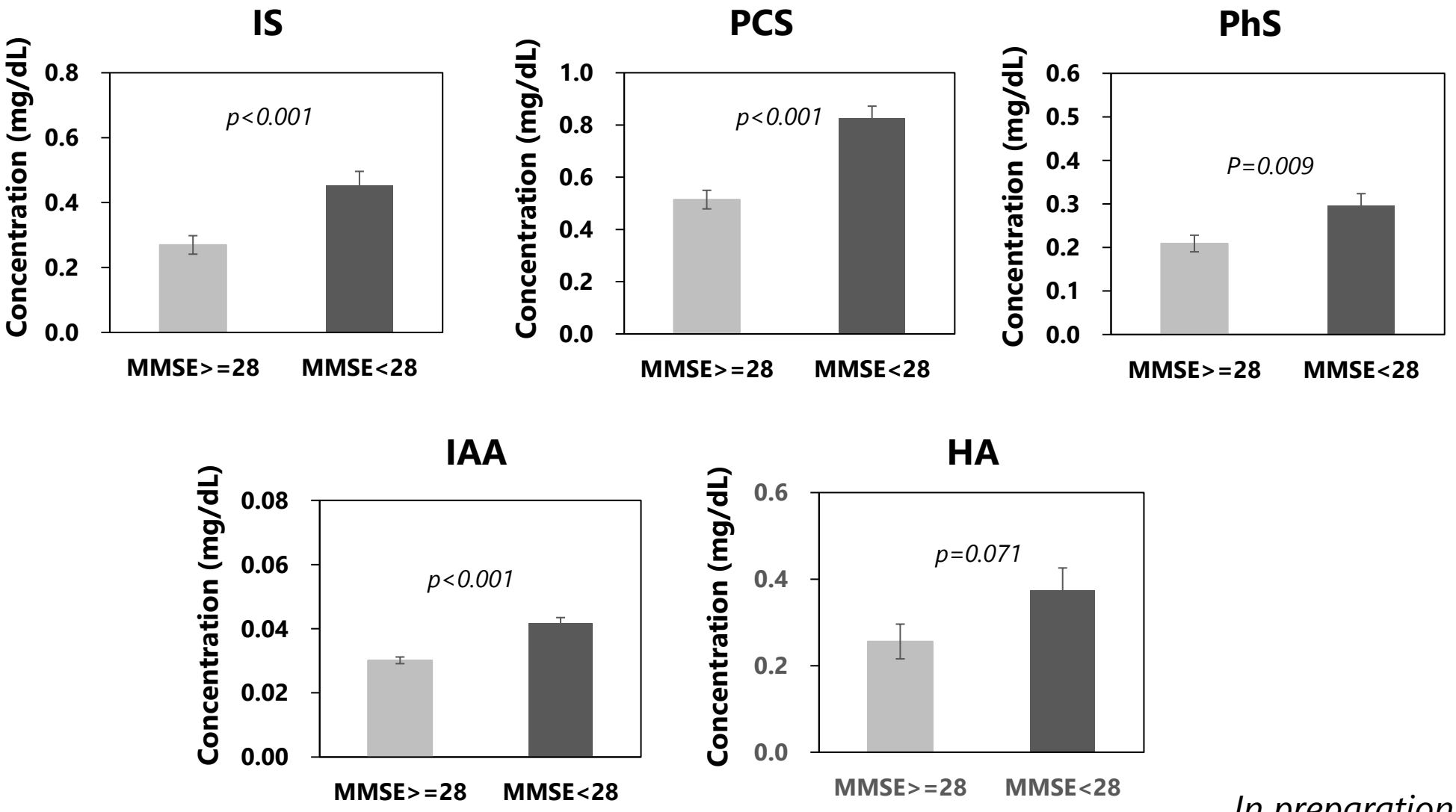
Sato E, Toxins, 2017

Cognitive function and CKD stages



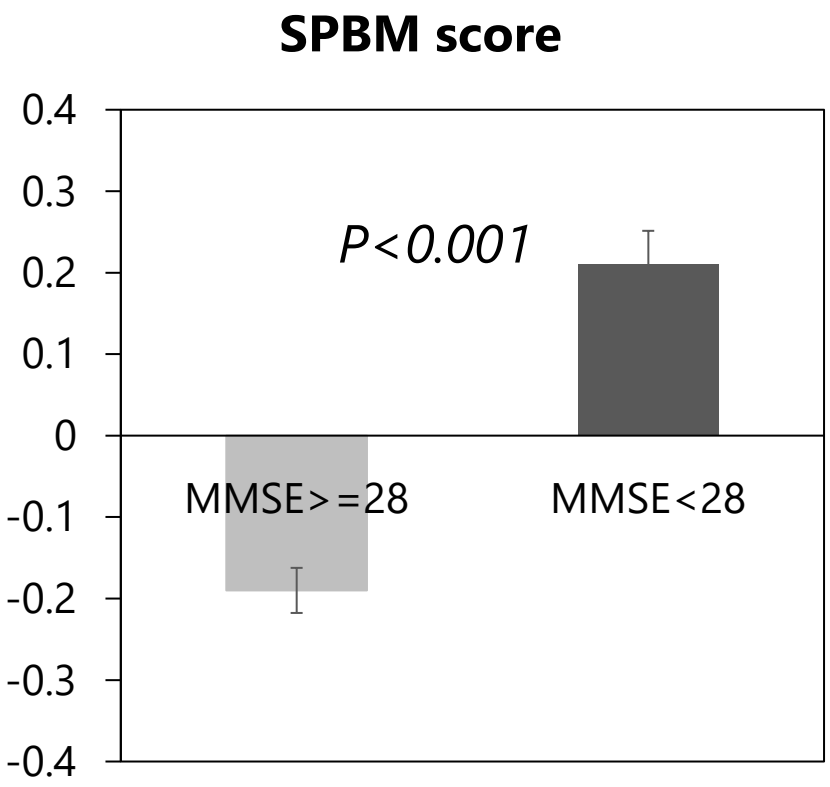
In preparation

Mild cognitive impairment and SPBMs



In preparation

SPBM score and mild cognitive impairment

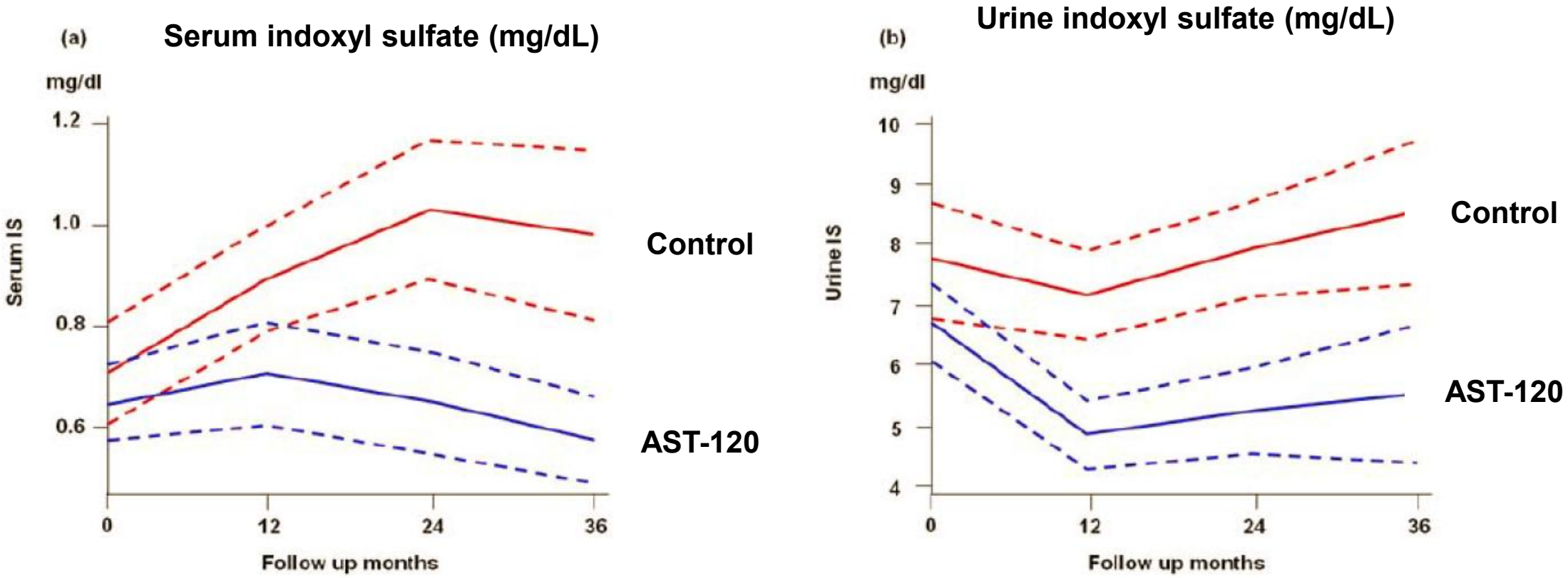


Independent variables	Coefficient	SE	OR	OR [Lower]	OR [Upper]	P value
SPBM score	**0.274**	**0.071**	**0.760**	**0.661**	**0.874**	**<.001**
eGFR	**-0.159**	**0.046**	**0.853**	**0.779**	**0.934**	**<.001**
β_2-m	**0.047**	**0.012**	**0.955**	**0.933**	**0.976**	**<.001**

Adjusted with gender, age, systolic blood pressure, body mass index, diabetes, and history of cerebrovascular disease

In preparation

AST-120 reduces the serum and urinary indoxyl sulfate in non-dialysis CKD patients



Cha R, Clin J Am Soci Nephrol, 2016

Use of AST-120 decreased the cardiovascular events in non-dialysis CKD patients

Table 5. Cox proportional-hazard analysis for major adverse cardiovascular events

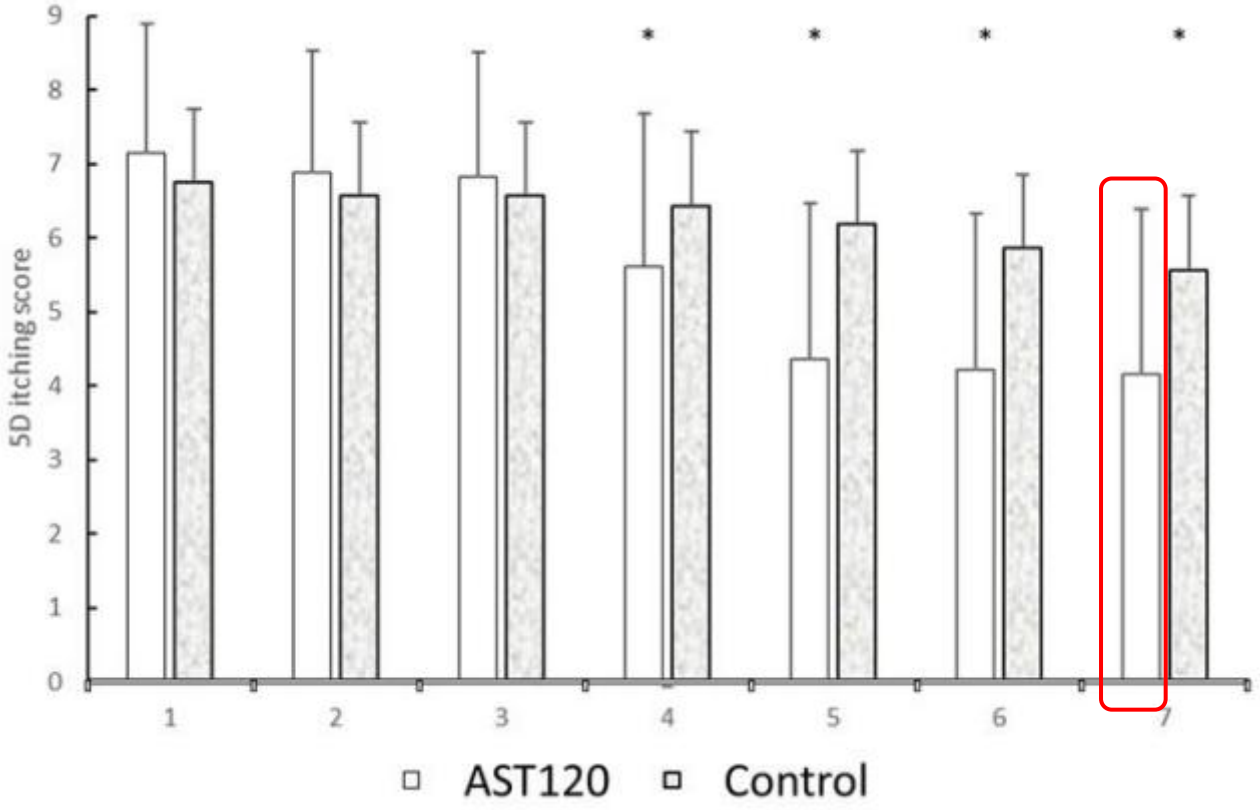
Variable	Major adverse cardiovascular events		
	HR	95% CI	*P*
Age (yr)	1.05	1.02–1.08	0.002
Gender (female)*	0.77	0.39–1.55	0.47
CKD cause (diabetic nephropathy)†	2.09	1.05–4.14	0.035
Urinary protein (g/g Cr)	0.94	0.79–1.12	0.46
CKD stage 4‡	2.11	0.83–5.32	0.12
AST-120§	0.51	0.26–0.99	0.046

CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio.

Reference: *male, †non-diabetic nephropathy, ‡CKD stage 3, §control arm.

Cha R, Kidney Res Clin Pract, 2017

AST-120 decreases of Indoxyl sulfate and improves pruritus in hemodialysis patients



AST-120

Control

Indoxyl sulfate (μg/mL)

AST-120	42.8	→	→	→	→	→	32.9
Control	49.2	→	→	→	→	→	48.6

Wu CC, Aging, 2024

Uremic toxins and systemic complications in patients with kidney disease

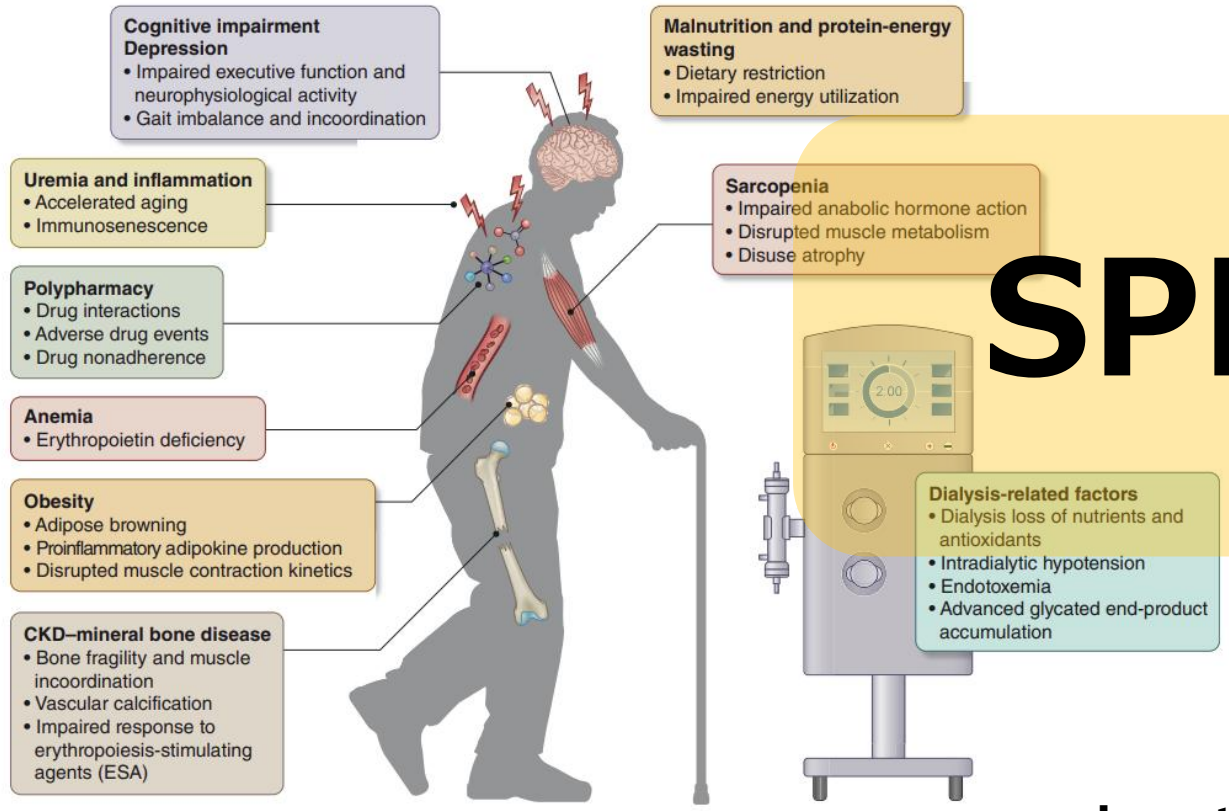
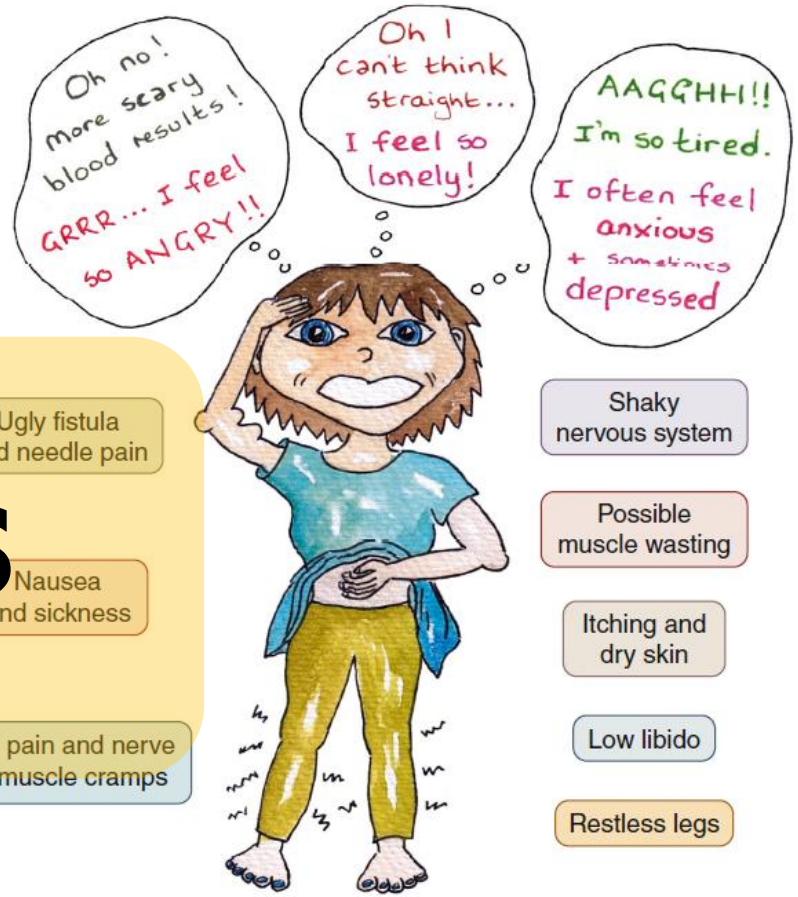


Figure 2 | Contributors to frailty in patients on dialysis. CKD, chronic kidney disease.

Chan GC, Kidney Int, 2024

SPBMs



Mehrotra R, Kidney Int, 2023

Investigate the more detailed toxicity of SPBMs
Promote measurement of SPBMs in clinical practice
Develop strategies to reduce SPBMs