Sarcopenia, Frailty, & Malnutrition:

A Diabolical Trio in the Presence of CKD

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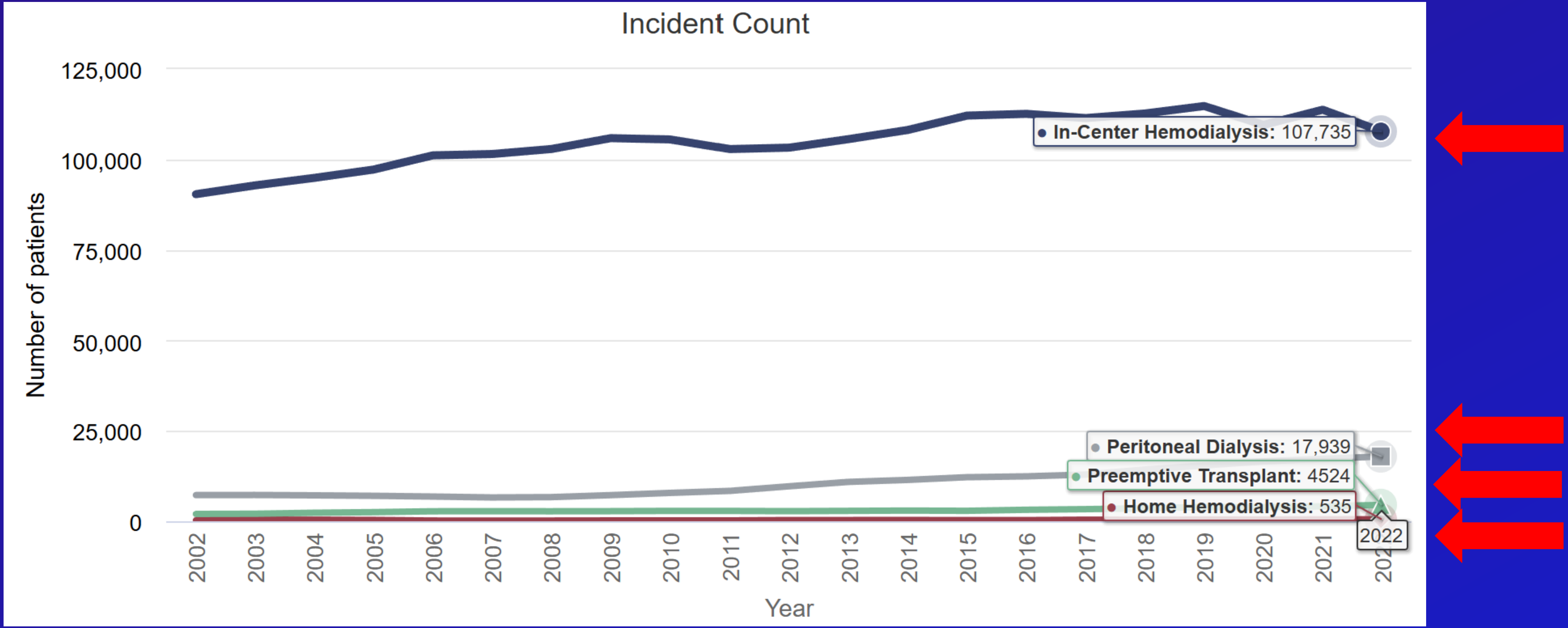
- Non-federal disclosures:
  - AstraZeneca, Dexcom, Fresenius, Vifor (past)
  - Editor-in-Chief, *Clinical Journal of the American Society of Nephrology*
- Federal disclosures: NIH study section

Objectives

- Review the scope of sarcopenia, frailty, and malnutrition-protein energy wasting (PEW) in CKD.
  - Nomenclature and definitions.
  - Epidemiology across spectrum of CKD.
- Discuss commonalities in risk factors and underlying mechanisms.
  - Overlapping adverse sequelae of sarcopenia, frailty, and PEW.
- Multi-modal treatment interventions to reduce complications.
  - Screening tools for early detection and intervention.

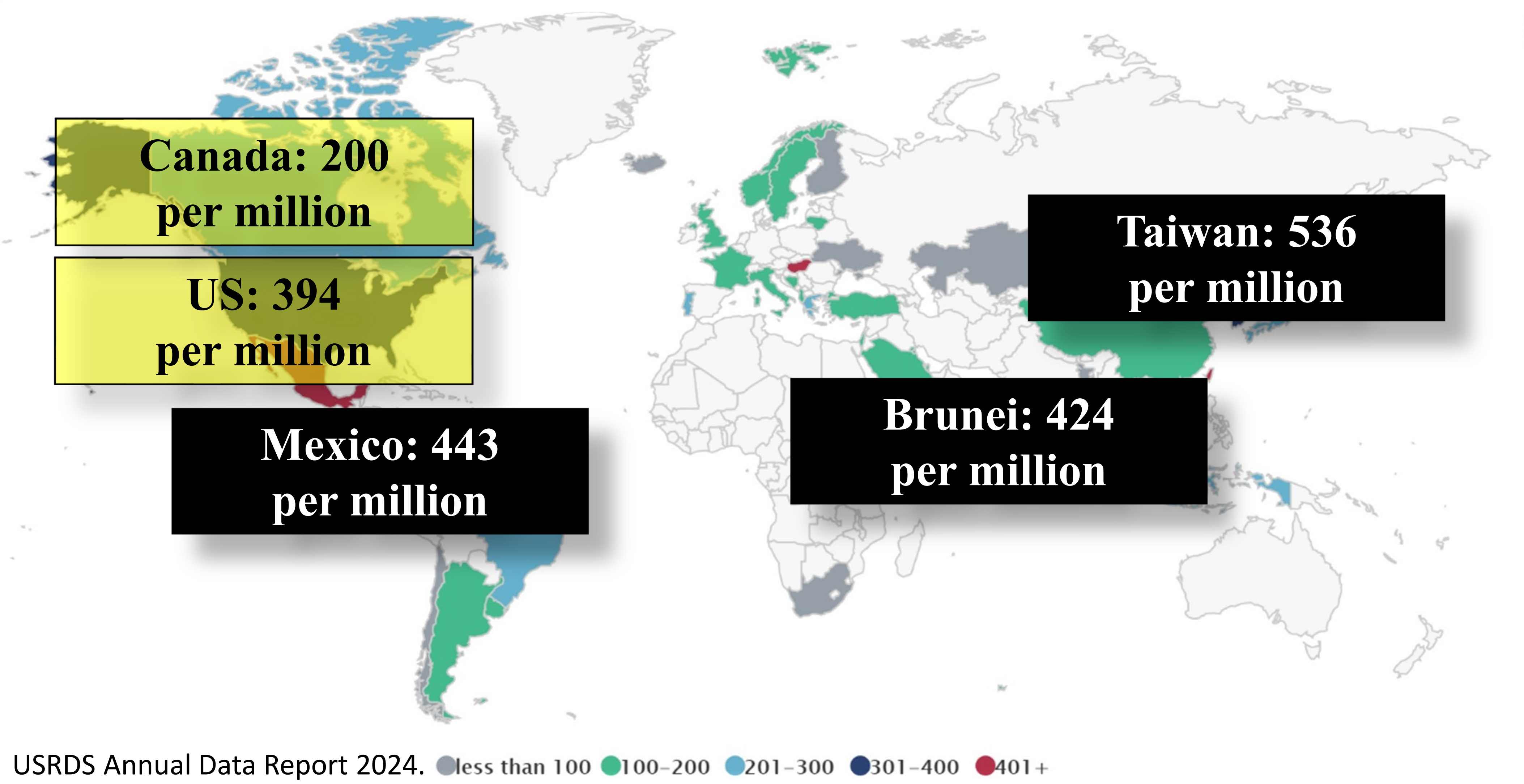
SCOPE OF DISEASE

Each year over ~130,000 patients in the US ***transition to ESKD***



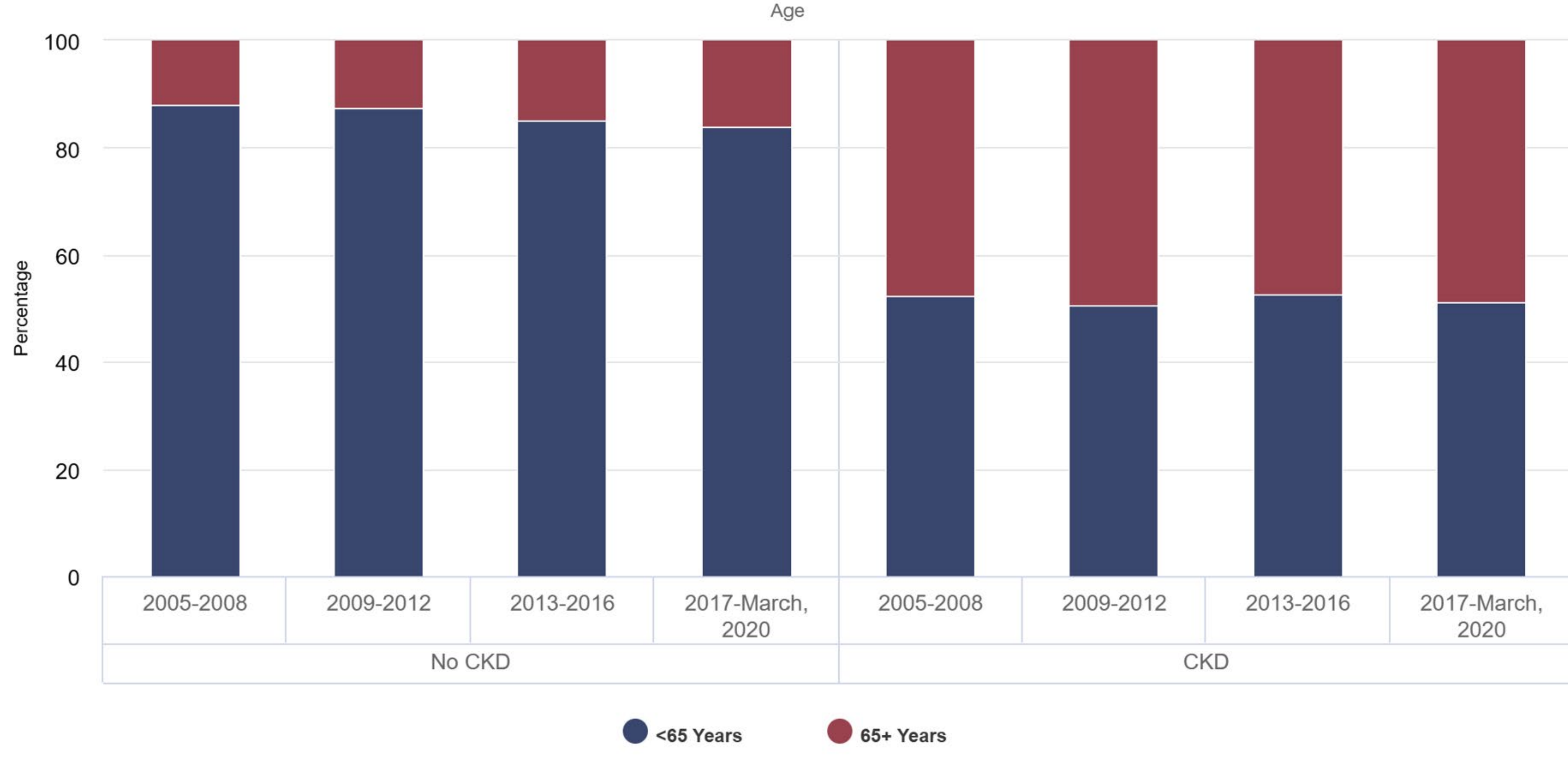
USRDS Annual Data Report 2024.

International comparisons of incident ESKD



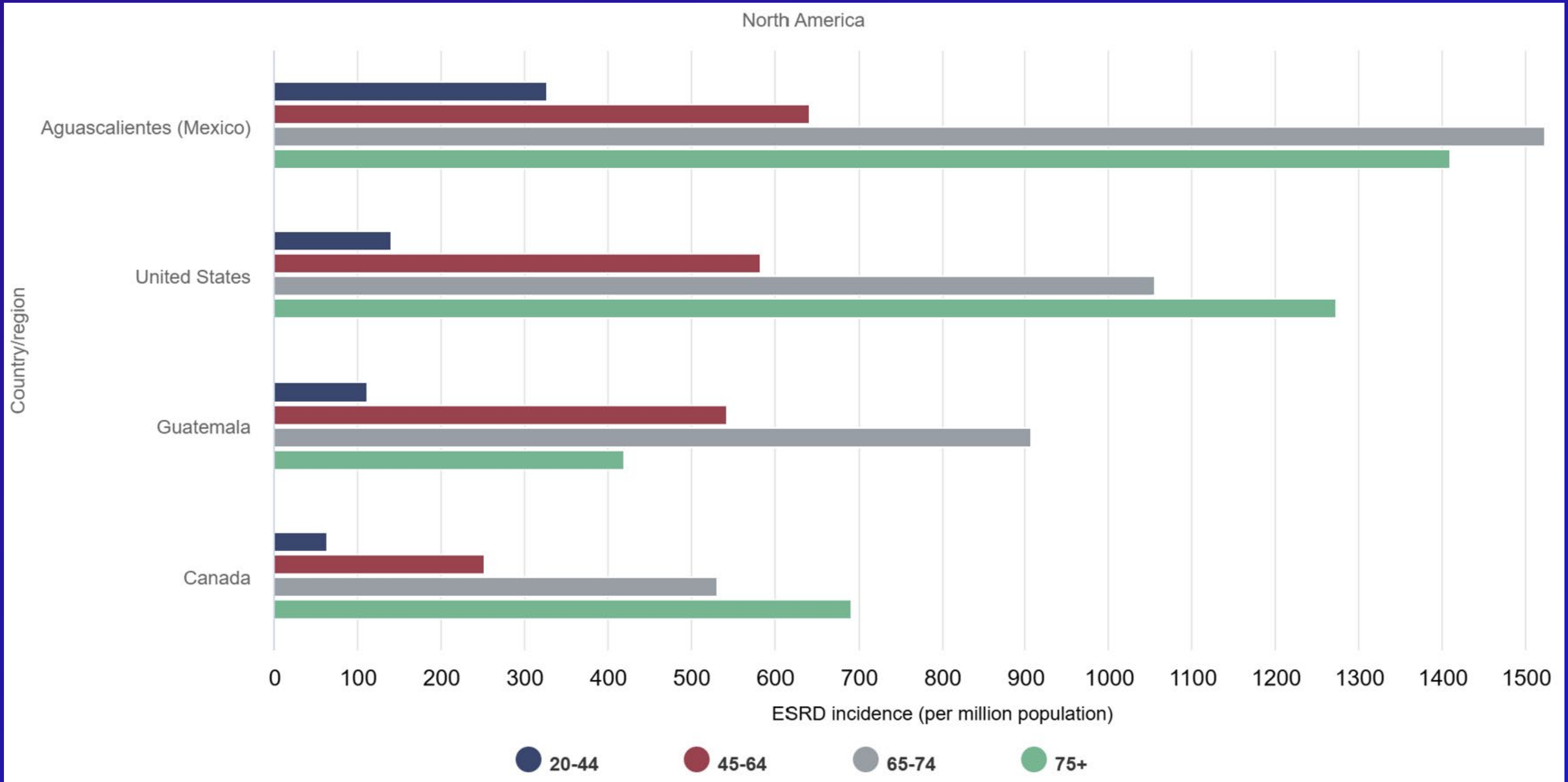
USRDS Annual Data Report 2024.

CKD disproportionately affects patients of elder age



USRDS Annual Data Report 2020.

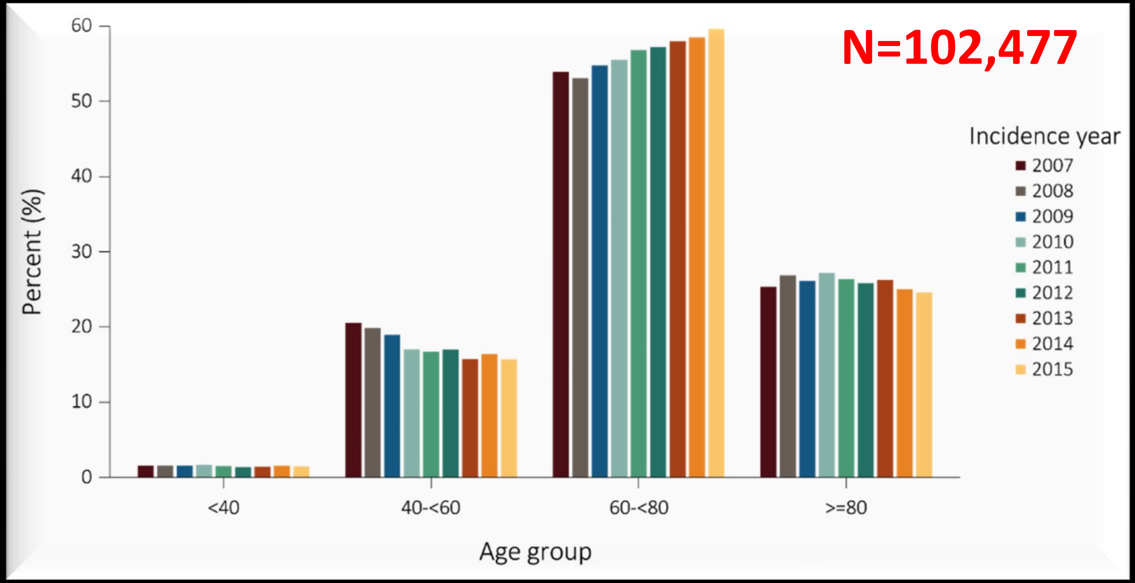
The global incident ESKD population is aging

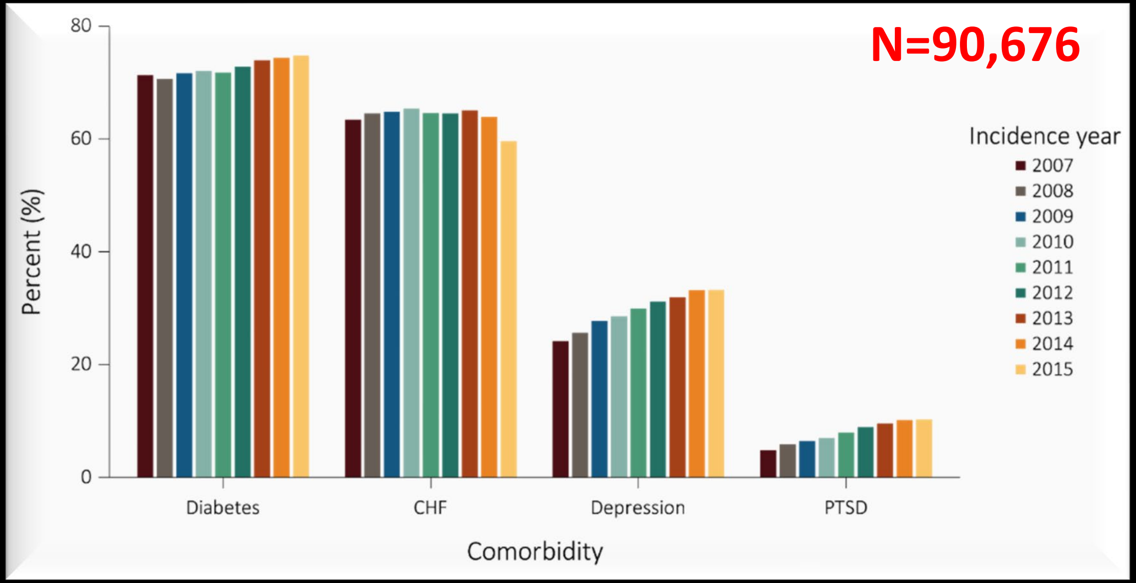


Across Western developed countries, highest incidence of treated ESRD in those 75+ years old

USRDS Annual Data Report 2024.
"Transition of Care in CKD" Special Study, USRDS Annual Data Report 2017.

Aging and ***ailing*** incident ESKD population





"Transition of Care in CKD" Special Study, USRDS Annual Data Report 2017.

Sarcopenia, Frailty, & Malnutrition-PEW

SARCOPENIA

- ✓ Loss of muscle mass, strength, and/of performance
- ✓ Does not require underlying illness

FRAILTY

- ✓ Physiologic decline
- ✓ Vulnerability to adverse health outcomes

MALNUTRITON & PROTEIN ENERGY WASTING

- ✓ Insufficient dietary intake
- ✓ Increased protein catabolism

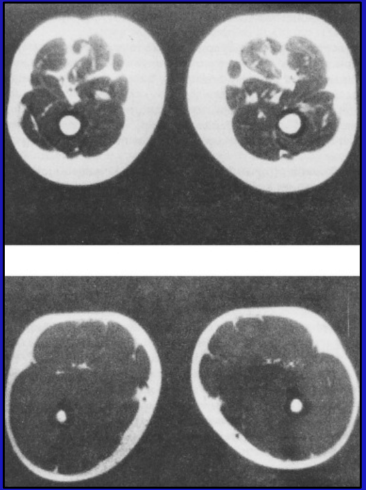
SARCOPENIA

Origins of sarcopenia

- Coined by Dr. Irwin Rosenberg in 1988
- Greek roots:
  - "*Sarx*" = flesh + "*Penia*" = loss
- Recognition of sarcopenia as a public health concern

> *"No decline with age is more dramatic or potentially more functionally significant than the decline in lean body mass."*

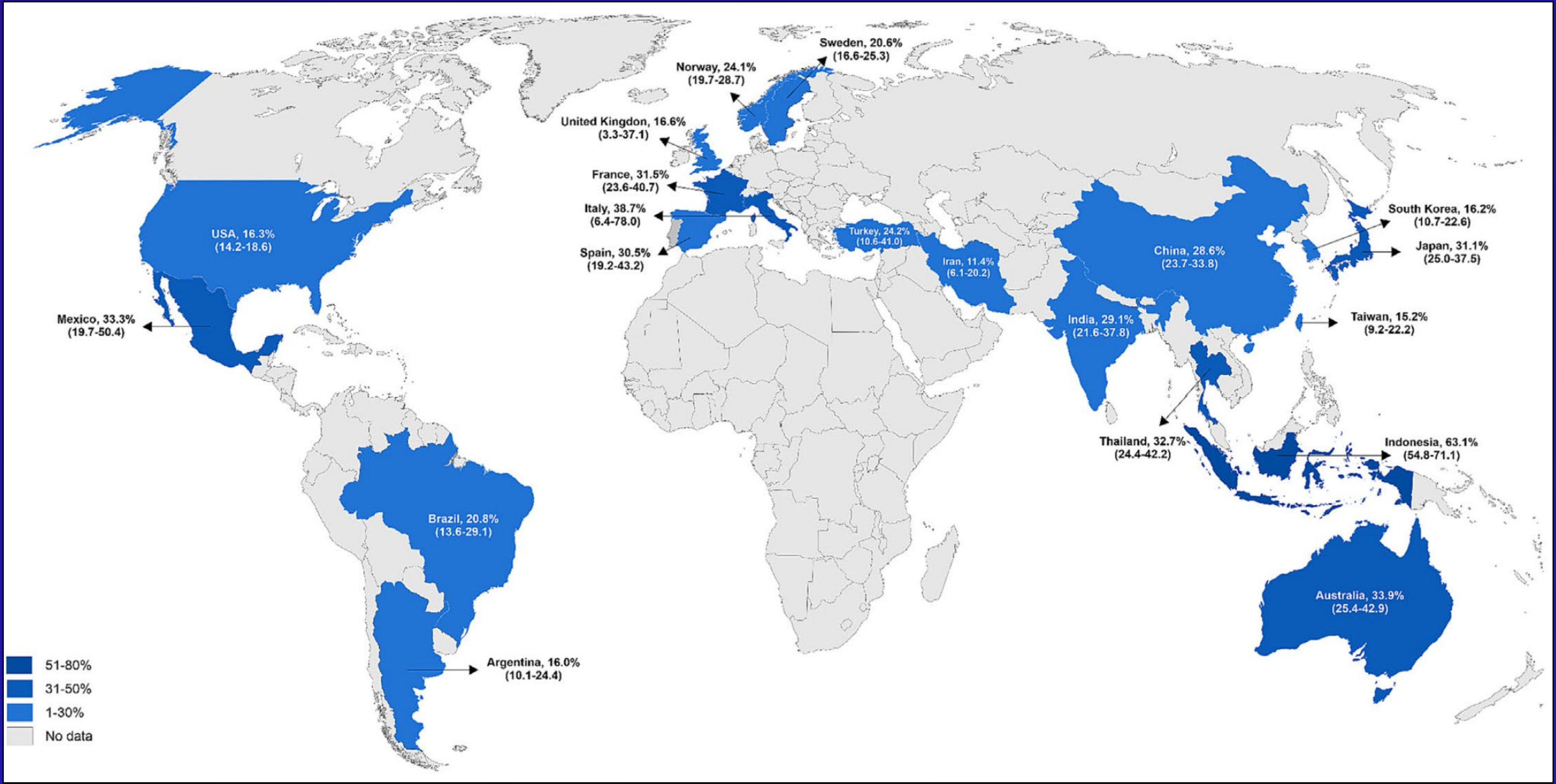
Dr. Irwin Rosenberg, Director, Jean Mayer USDA Human Nutrition Research Center on Aging, Tufts University



OLDER

YOUNGER

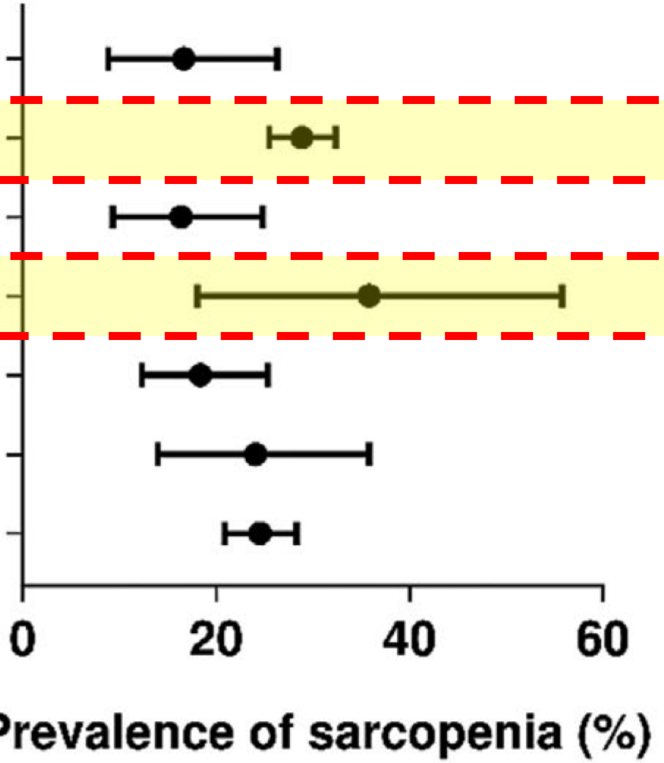
High burden of sarcopenia in CKD worldwide



Duarte et al. ***JCSM*** 2024.

Prevalence of sarcopenia in patients with chronic kidney disease: a global systematic review and meta-analysis

Marvery P. Duarte[1,2], Lucas S. Almeida[1], Silvia G.R. Neri[1], Juliana S. Oliveira[3,4], Thomas J. Wilkinson[5]*, Heitor S. Ribeiro[1,2] & Ricardo M. Lima[1]



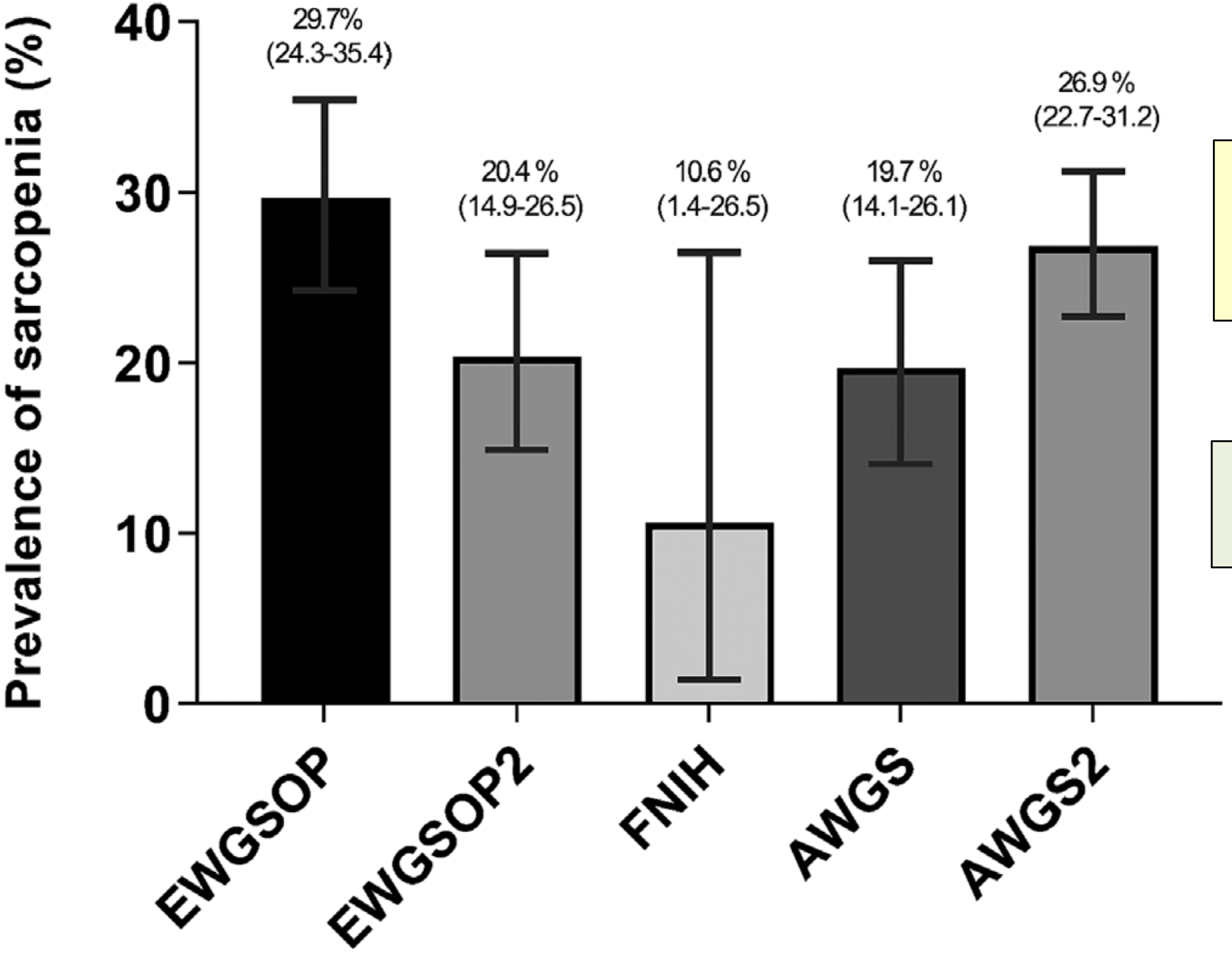
	No. of studies	No. of patients	Prevalence (%) Random effects (95% CI)	I^2
Non-dialysis	19	12,908	16.7 (8.9-26.3)	99.0
Hemodialysis	63	18,190	28.8 (25.5-32.3)	95.8
Peritoneal dialysis	8	1,283	16.3 (9.3-24.8)	92.6
Dialysis (HD + PD)	4	662	35.8 (18.1-55.8)	94.4
Kidney transplant	13	1,672	18.4 (12.3-25.3)	91.6
CKD-grouped	7	1,475	24.0 (13.9-35.8)	95.4
Overall	114	36,190	24.5 (20.9-28.3)	98.4

Duarte et al. *JCSM* 2024.

Varying prevalences of sarcopenia by definition

European Working Group on Sarcopenia in Older People

Asian Working Group for Sarcopenia



Foundation for the National Institutes of Health

International Working Group on Sarcopenia

Duarte et al. *JCSM* 2024.

Definitions of sarcopenia across international groups

Sarcopenia = Presence of low appendicular lean skeletal muscle mass with low muscle strength and/or low physical performance (EWGSOP)

	EWGSOP (2010)	EWGSOP2 (2018)	FNIH (2014)	AWGS (2014)	AWGS (2019)
Muscle mass					
DXA	<7.26 kg/m2 (M) <5.5 kg/m2 (F)	<7.0 kg/m2 (M) <5.5 kg/m2 (F)	<0.789 m2 (M) <0.512 m2 (F)	<7.0 kg/m2 (M) <5.4 kg/m2 (F)	<7.0 kg/m2 (M) <5.4 kg/m2 (F)
BIA	<8.87 kg/m2 (M) <6.42 kg/m2 (F)			<7.0 kg/m2 (M) <5.7 kg/m2 (F)	<7.0 kg/m2 (M) <5.7 kg/m2 (F)
Muscle strength					
Handgrip	<30 kg (M) <20 kg (F)	<27 kg (M) <16 kg (F)	<26 kg (M) <16 kg (F)	<26 kg (M) <18 kg (F)	<28 kg (M) <18 kg (F)
Chair stand		$15 s			
Muscle performance					
Gait speed	<0.8 m/s	≤0.8 m/s	<0.8 m/s	<0.8 m/s	<1.0 m/s
400-m walk test		Non-completion or ≥6 min for completion			
Chair stand					≥12 s

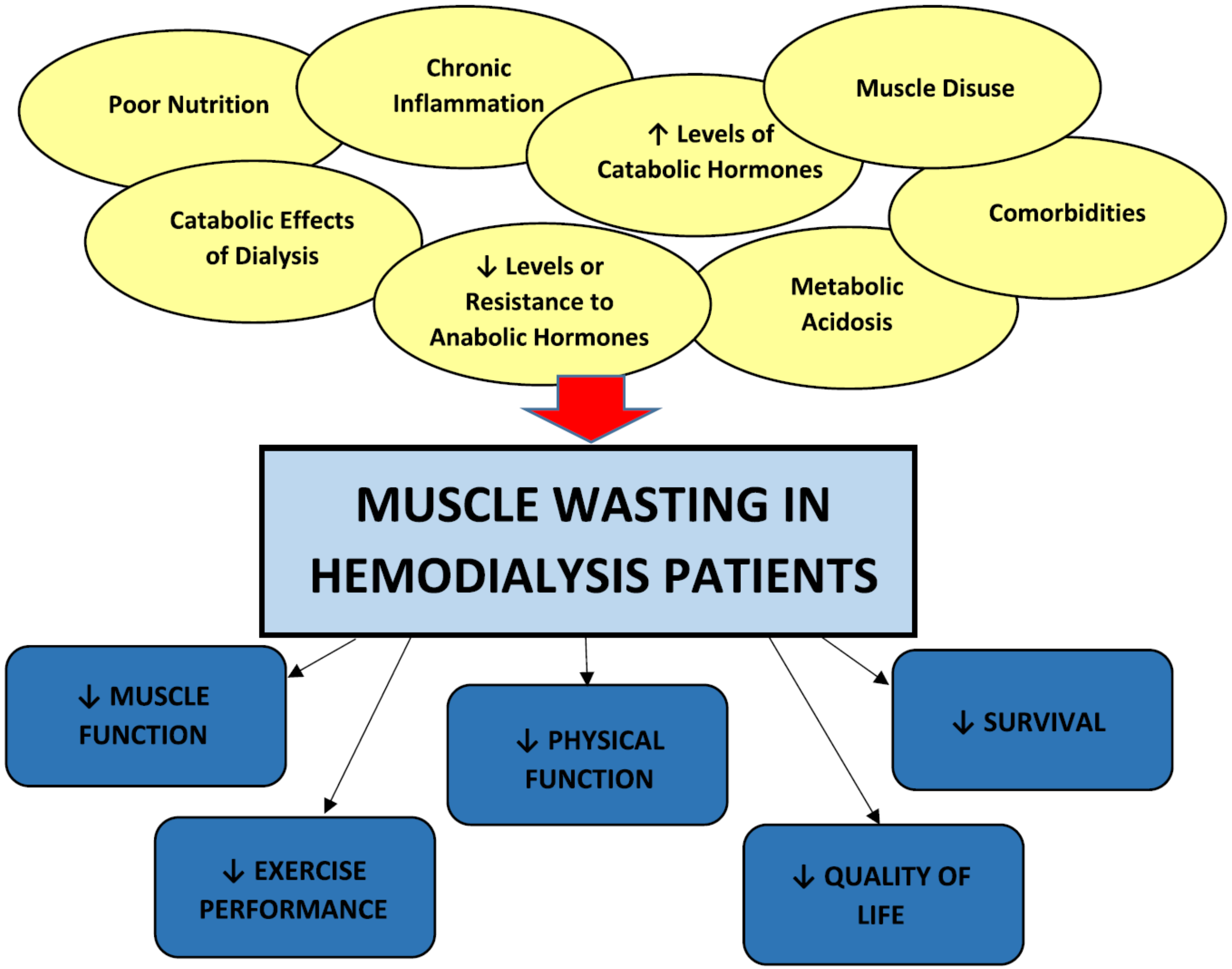
CKD-related vs. aging-related sarcopenia

	SECONDARY SARCOPENIA	PRIMARY SARCOPENIA
	CKD-related sarcopenia	Ageing-related sarcopenia
Muscle protein degradation	Increased	No change
Muscle protein synthesis	Decreased	Decreased
Resting energy expenditure	Increased/unchanged	Unchanged
Inflammation	Increased	Increased or unchanged
Insulin resistance	Present	Present
Body fat	Unchanged, increased or decreased	Normally increased
Muscle fiber change	Atrophy in type I and II fibers	Preferential loss of type II fibers

Treatment goals may differ from CKD- vs. aging-related sarcopenia.

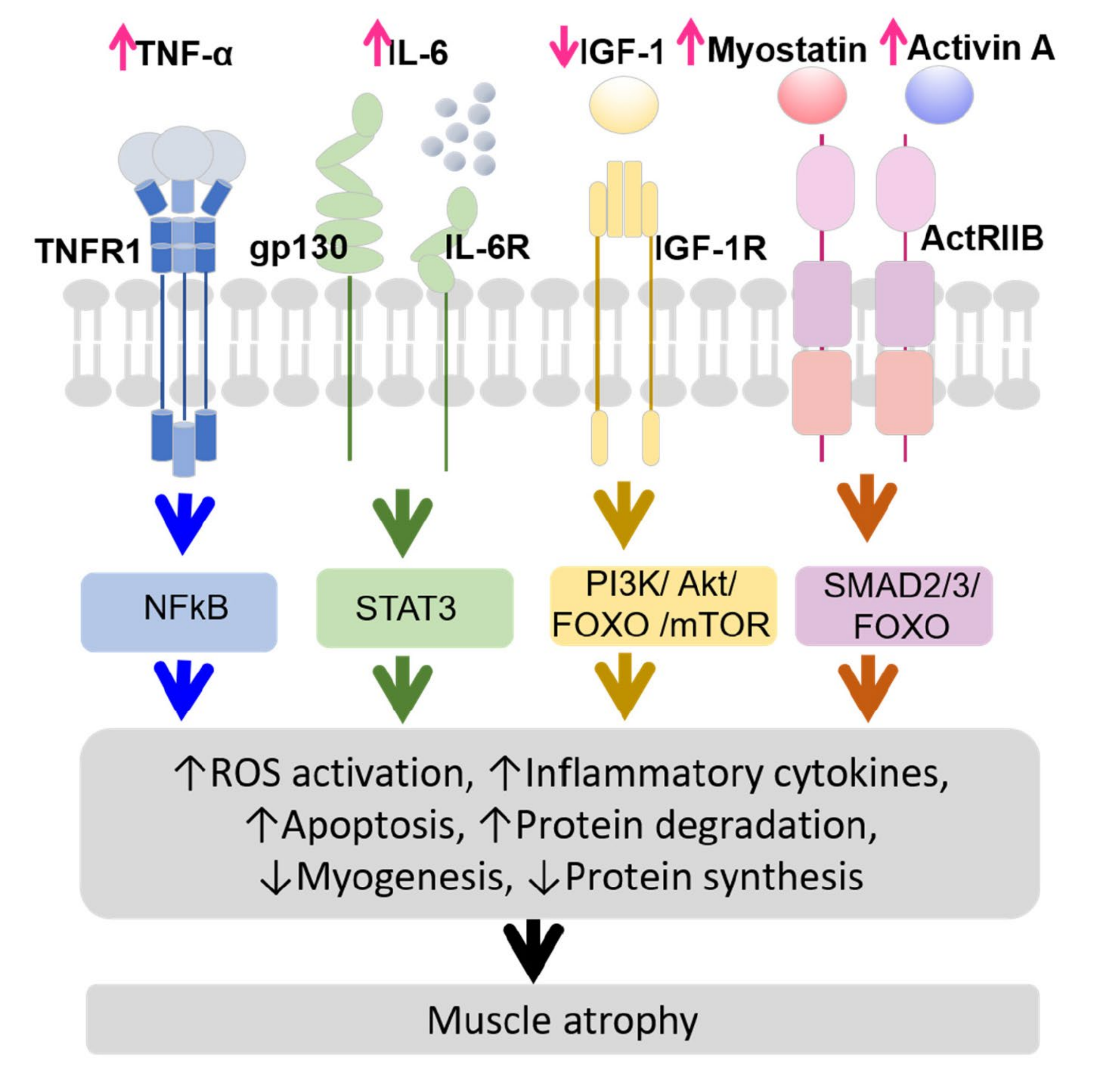
Sabatino et al. ***Jl Nephrology*** 2021.

Unique risk factors for muscle wasting in CKD



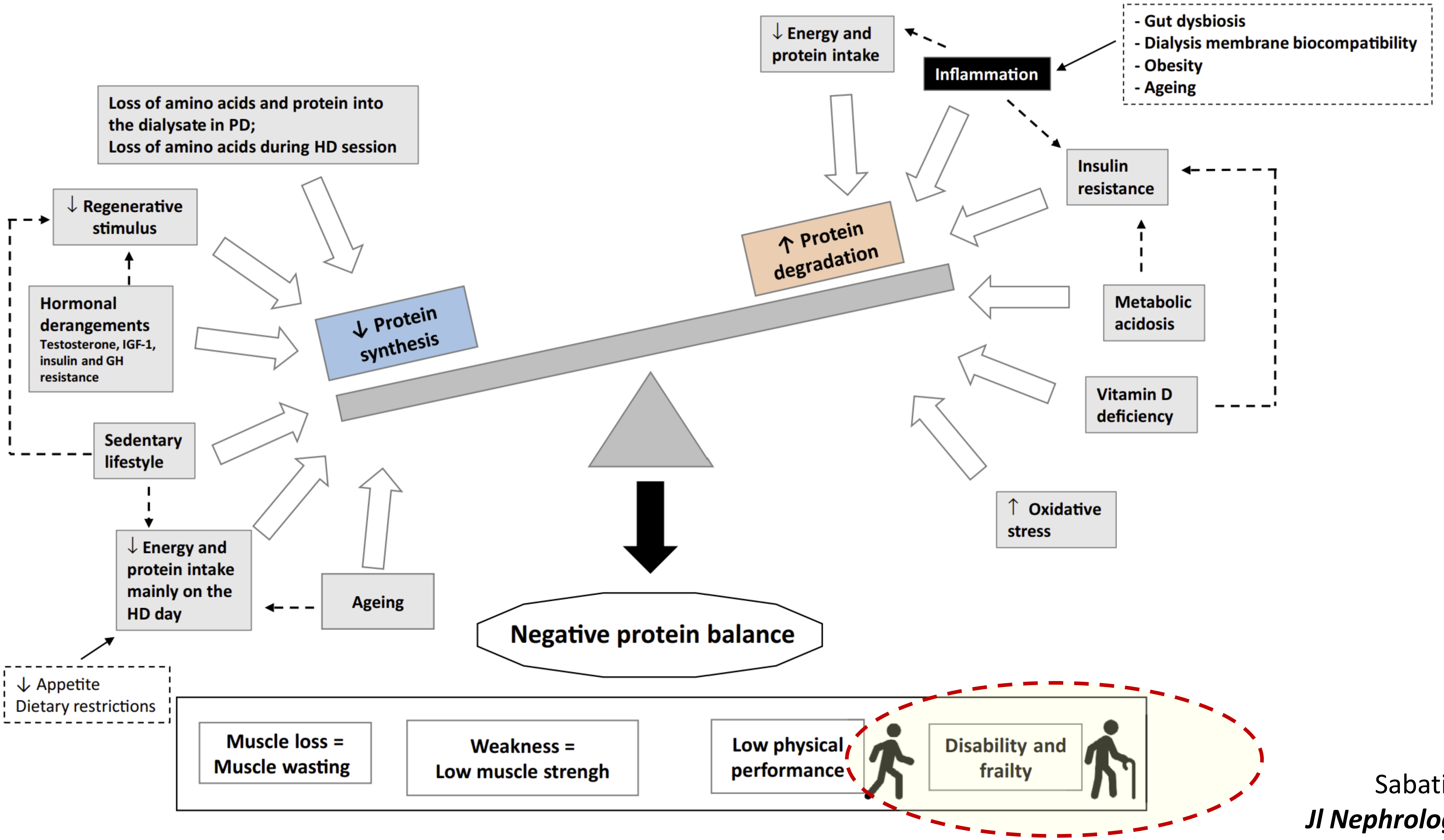
Rhee, Kalantar-Zadeh. ***JCSM*** 2014.

Molecular mechanisms of muscle atrophy in CKD



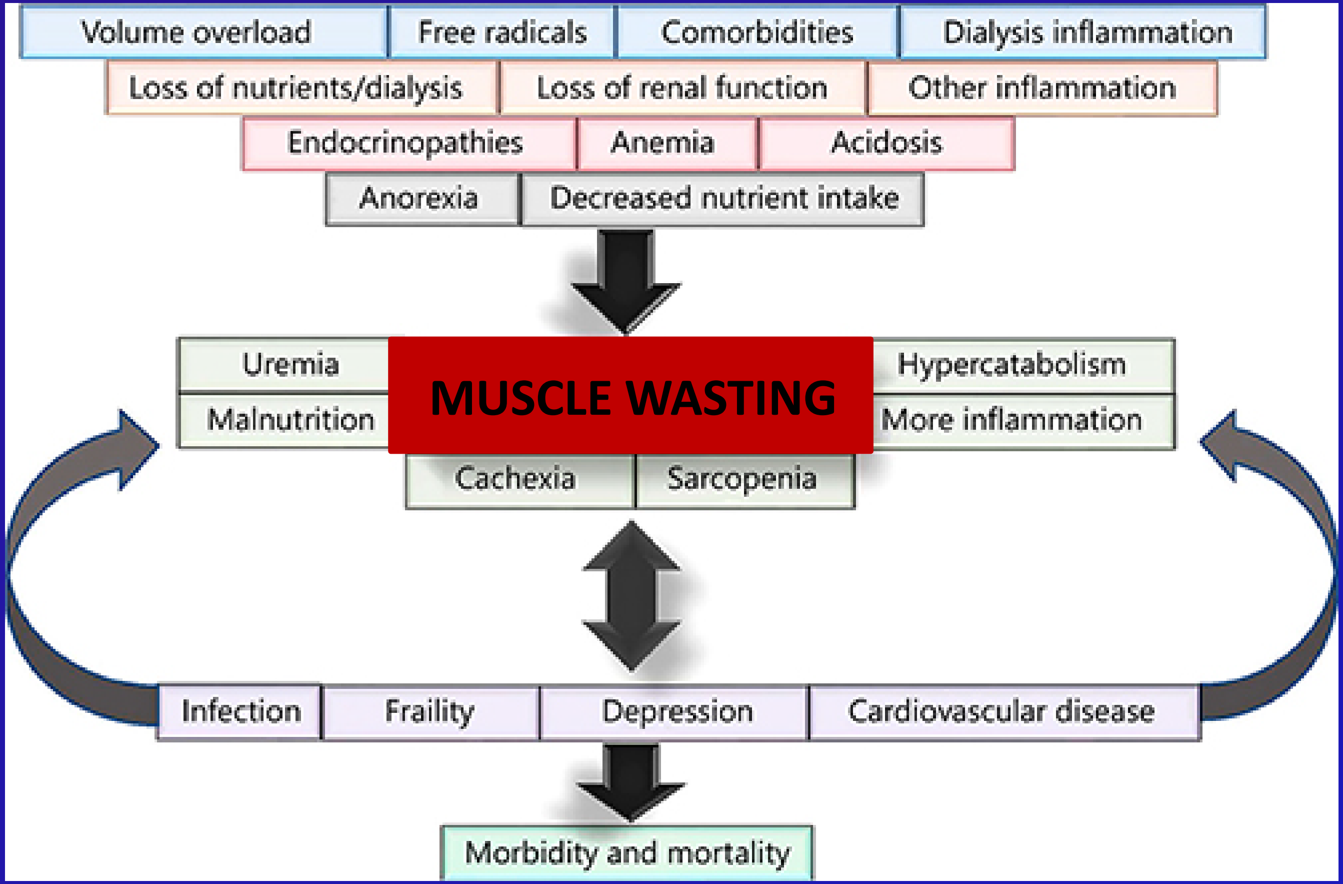
Tsai et al. ***Biomedicines*** 2025.

Multiple factors leading to negative protein balance



Sabatino et al.
Jl Nephrology 2021.

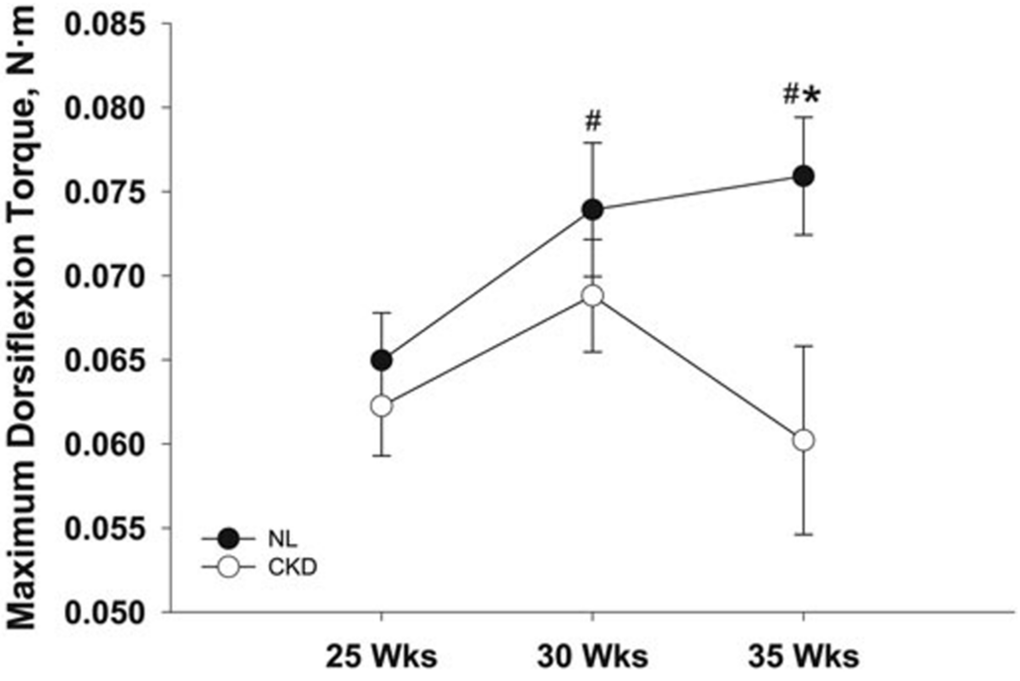
Muscle wasting in CKD associated with worse survival, physical function, and HRQOL



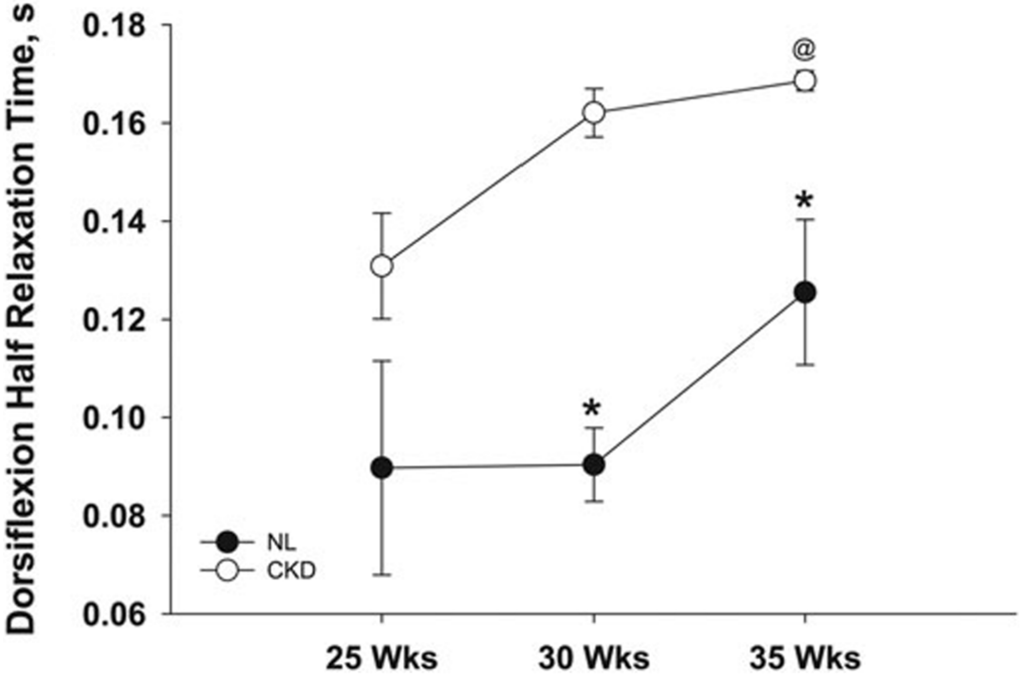
Hanna, Ghobry, Wassef, Rhee, Kalantar. ***Blood Purif*** 2020.
Kalantar, Rhee, Sim, Stenvinkel, Anker, Kovesdy. ***JCSM*** 2013.

In experimental models of CKD, **muscle function** declines without loss of muscle mass

↓'ed muscle strength (muscle torque)



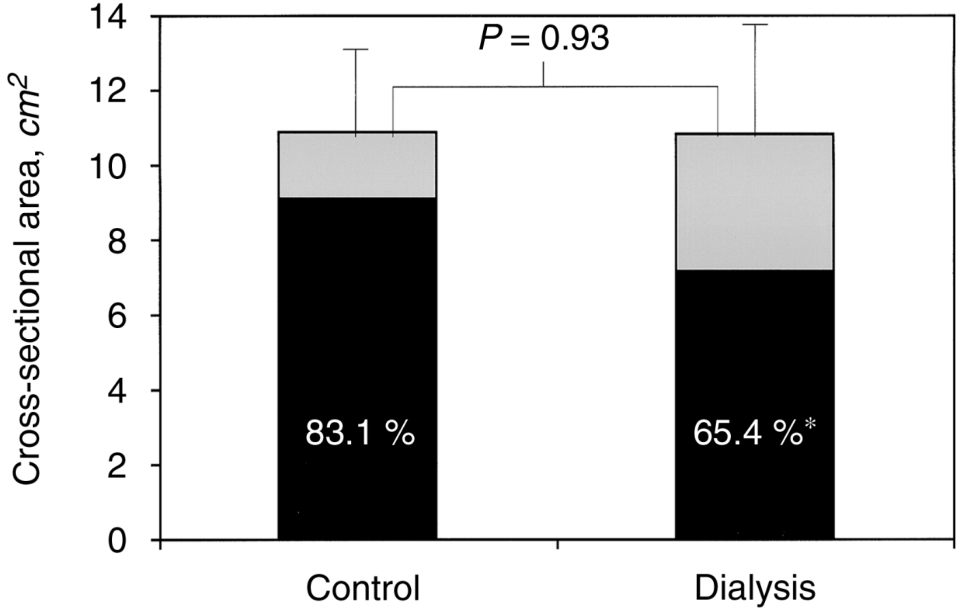
↑'ed half-relaxation time



Cy/+ rat

Organ et al. ***NDT*** 2015.

Impaired muscle quality may account for loss of muscle function independent of muscle mass



Variable	Dialysis subjects (*N* = 22)	Controls (*N* = 17)	*P* value
Total CSA *cm*²	10.8 ± 2.6	10.9 ± 2.2	0.93
Contractile CSA *cm*²	7.2 ± 3.1	9.1 ± 2.0	0.02
Noncontractile CSA *cm*²	3.7 ± 2.3	1.8 ± 0.5	0.001
MVC *N*	169.6 ± 65.5	217.7 ± 69.1	0.03
CAR	0.94 ± 0.12	0.96 ± 0.09	0.66
MVC/total CSA	15.0 ± 4.8	19.7 ± 4.6	0.003
MVC/contractile CSA	21.9 ± 7.2	23.4 ± 5.3	0.48

Data are mean ± SD. Abbreviations are: CSA, cross-sectional area; MVC, maximal voluntary contraction; CAR, central activation ratio.

<u>In age- and sex-matched HD patients vs. controls:</u>

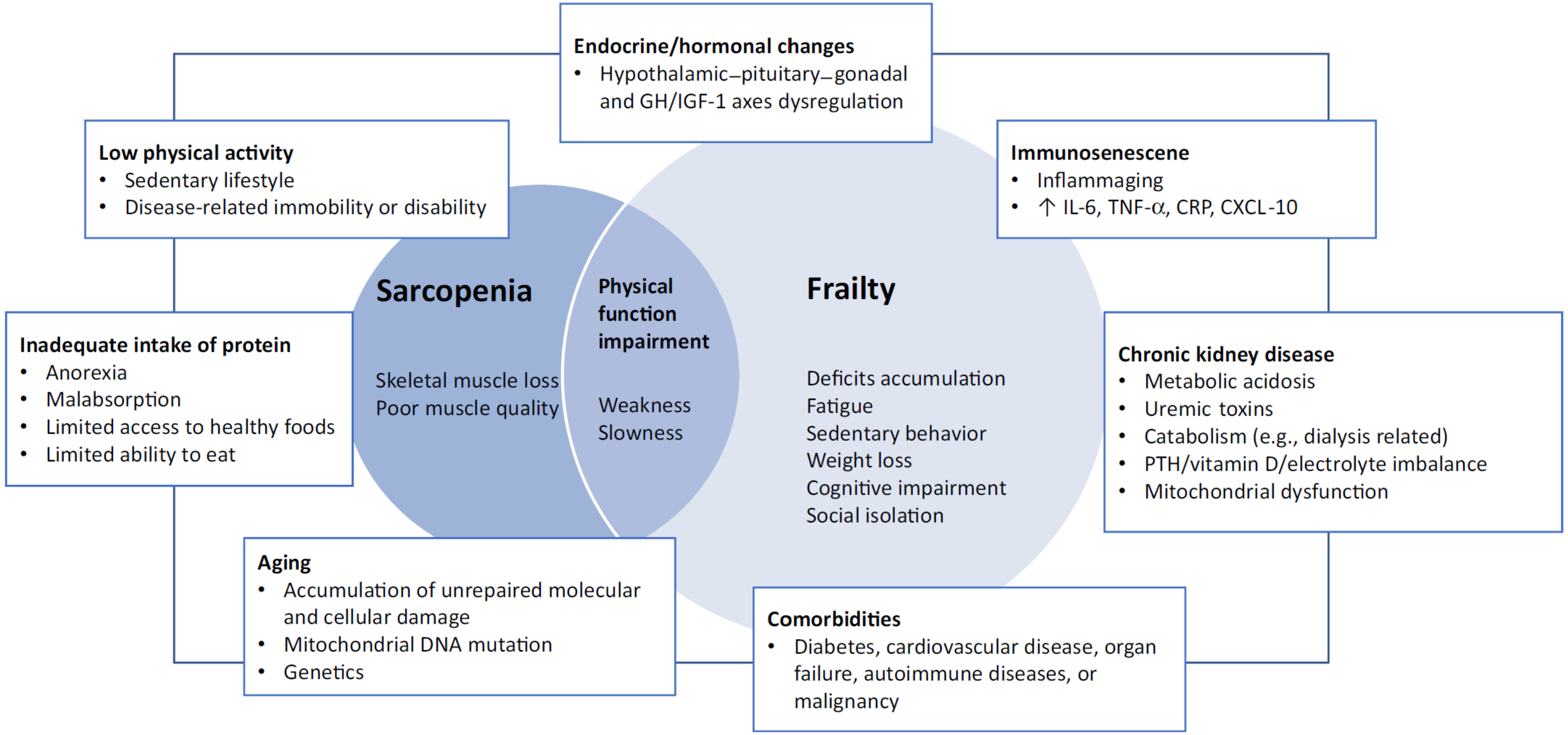
- ✓ *Total muscle cross-sectional area the same*
- ✓ *HD patients with less contractile tissue & more non-contractile tissue vs. controls*
- ✓ *HD patients had lower strength & gait speed vs. controls*

Johansen et al. ***KI*** 2003.

FRAILTY

Frailty = Syndrome of multi-system impairment with ↑ vulnerability to stressors

- Overlap between frailty & sarcopenia
- But, frailty constitutes a broader constitutional spectrum than sarcopenia
  - ➢ Physical, cognitive, and social
- Strongly associated with disability, hospitalization, & mortality



Wong et al. ***KI Reports*** 2021.
Roshanravan et al. ***AJKD*** 2017.

Two distinct models to conceptualize frailty

FRAILTY INDEX MODEL

(Rockwood)

Accumulation of deficits across multiple organ systems (i.e., cognition, mood)

More widely accepted in geriatrics community

FRAILTY PHENOTYPE MODEL

(Fried Phenotype)

Presence of ≥3 of 5 criteria:

- Weakness
- Slowness
- Shrinkage
- Exhaustion
- Low physical activity

Most commonly used frailty tool in CKD studies

Wong et al, ***KI Reports*** 2021.

Fried frailty phenotype tool & scoring

FRAILTY VARIABLE	DIAGNOSTIC CRITERIA
Weight loss	≥5% of body weight in last year
Exhaustion	Positive response to questions regarding effort required for activity
Weakness	Decreased grip strength
Slow walking speed	>6 to 7 seconds to walk 15 feet
Decreased physical activity	Males: <383 kcals expended/week Females: <270 kcals expended/ week

FRAILTY = ≥3 criteria

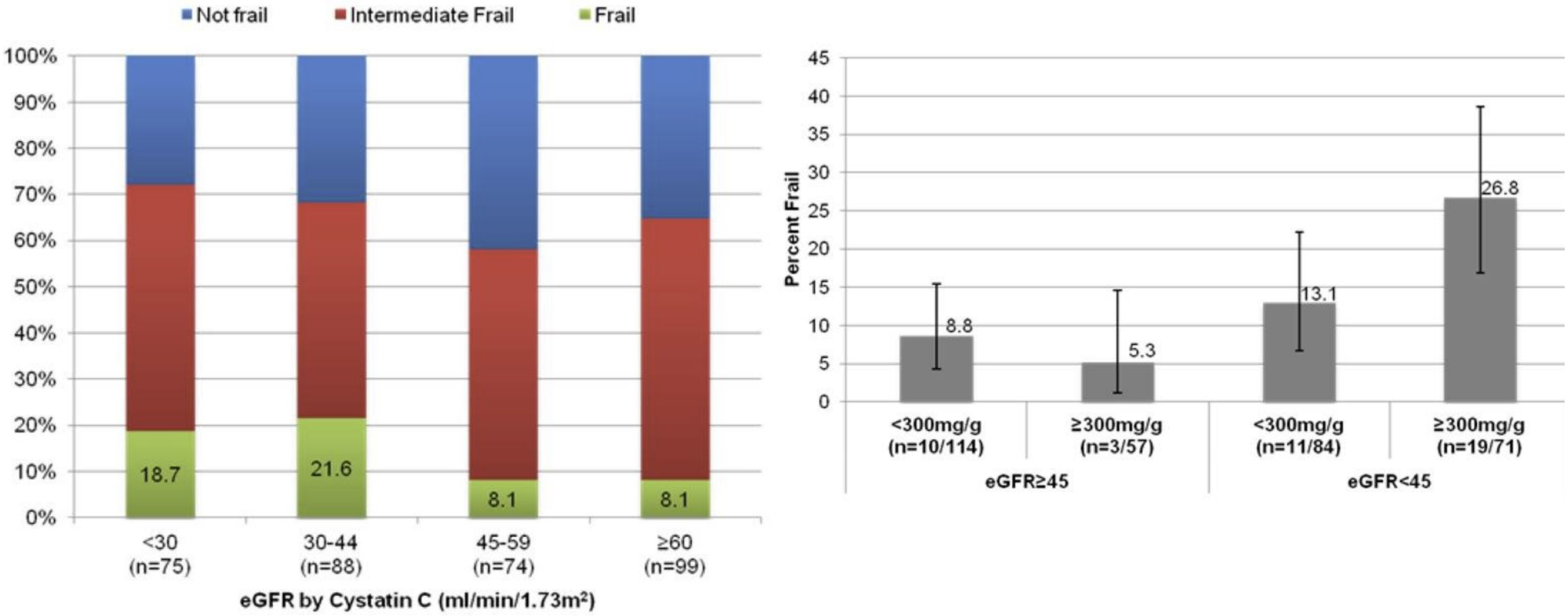
PRE-FRAILTY = 1-2 criteria

NOT FRAIL = 0 criteria

Physical inactivity most modifiable frailty component in CKD.

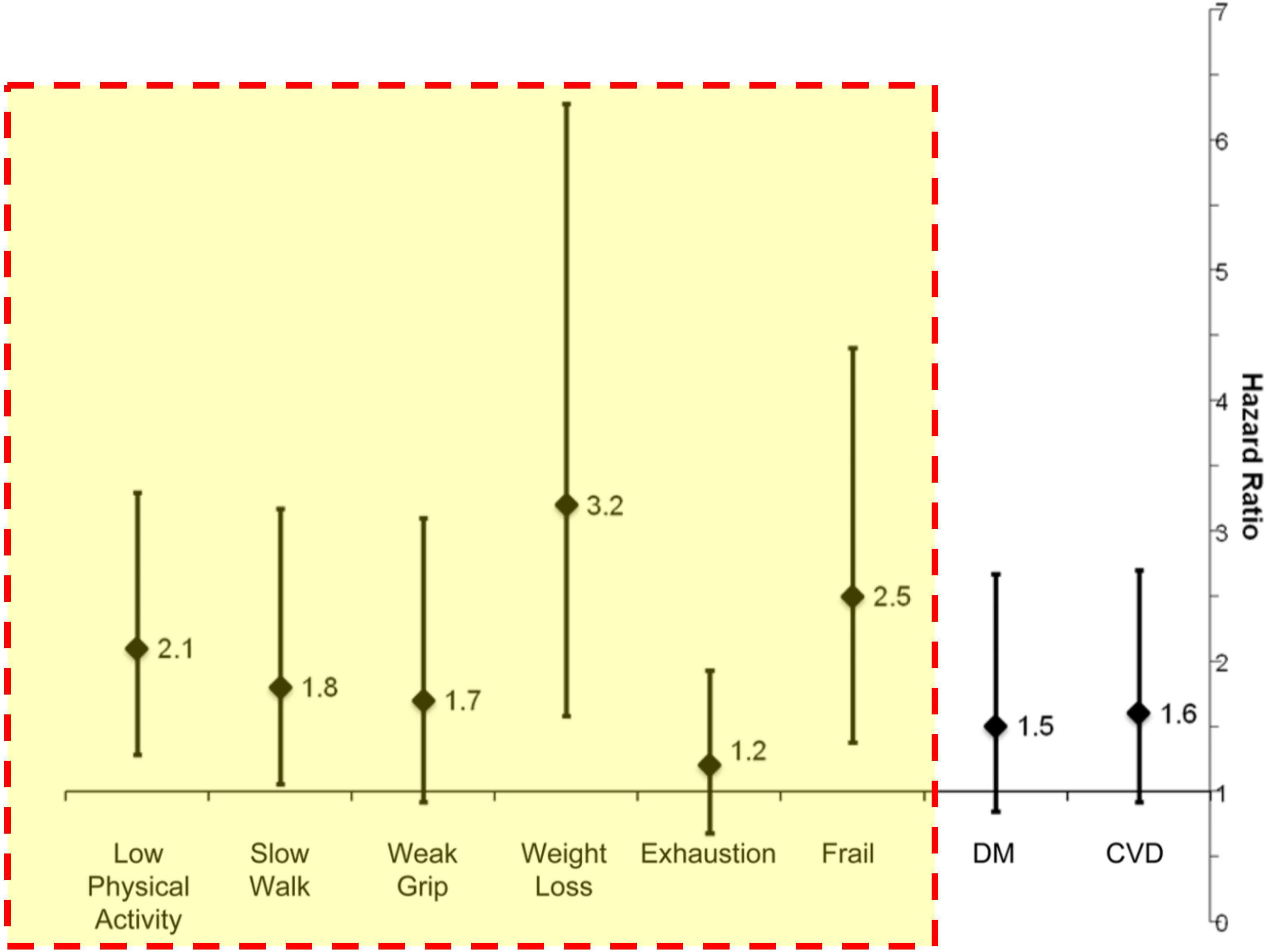
Fried et al, ***J Gerontol A Biol Sci Med Sci***, 2001.
Roshanravan et al, ***AJKD*** 2012.

Fried frailty phenotype across NDD-CKD stages



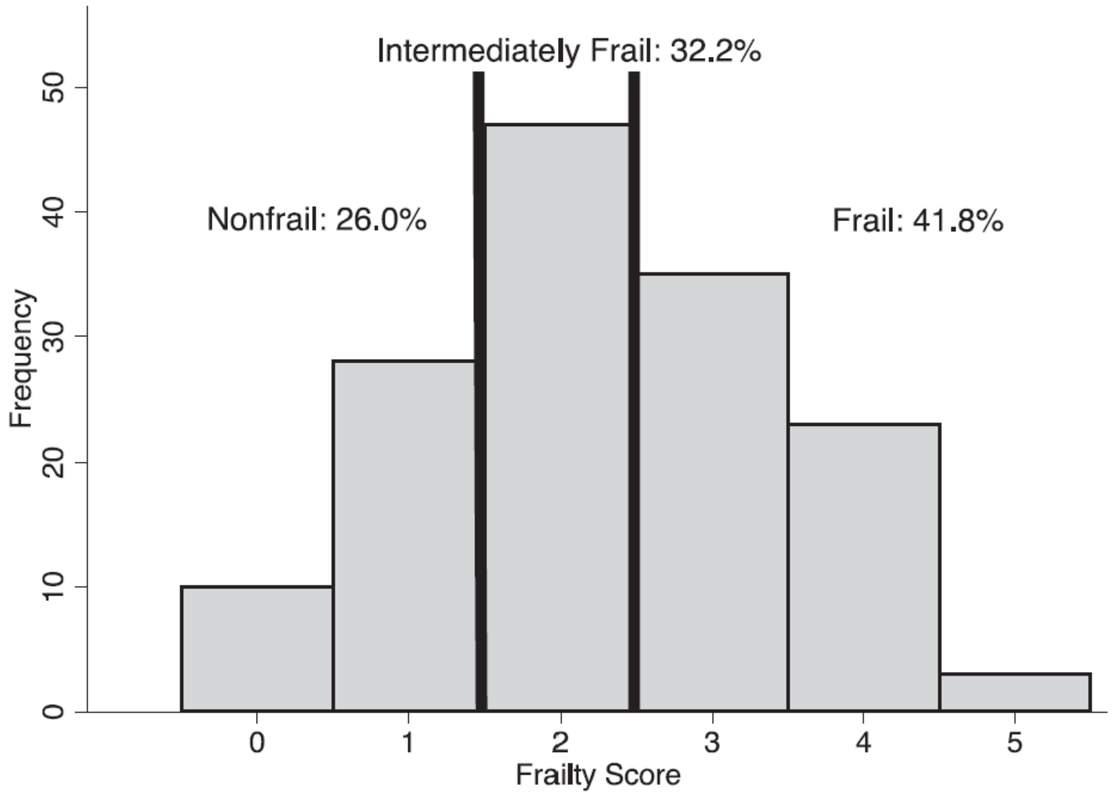
Roshanravan et al, ***AJKD*** 2012.

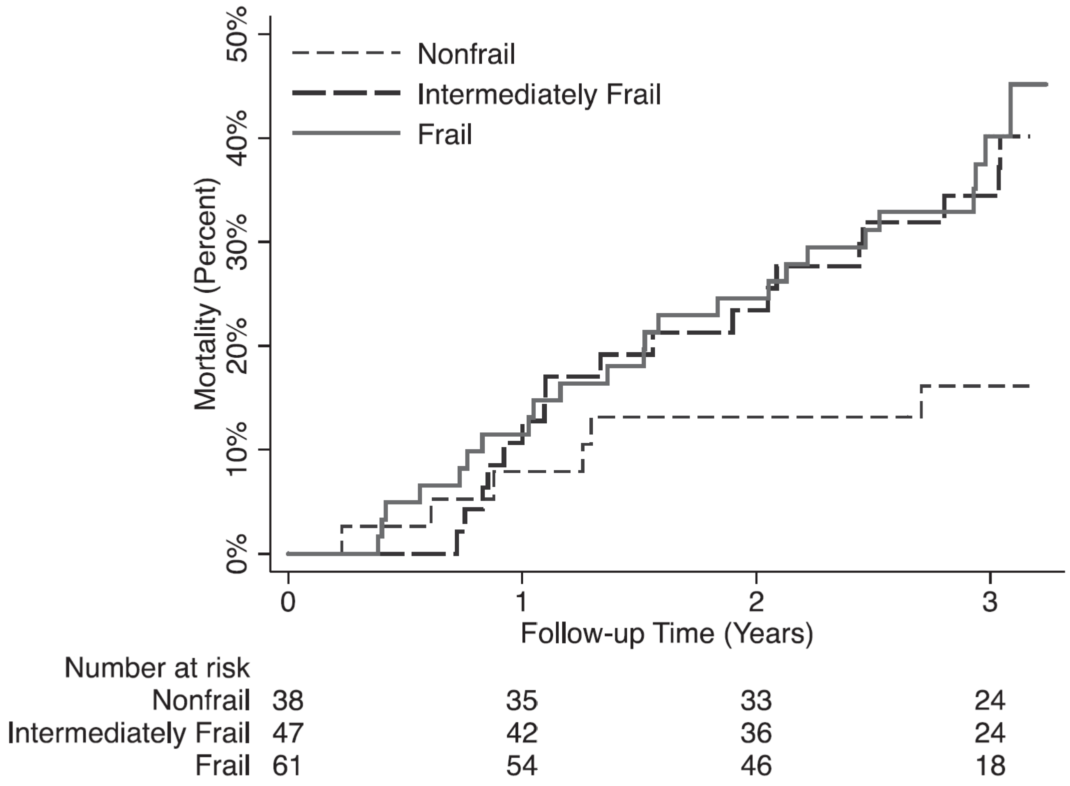
Risk of death or dialysis in NDD-CKD: Fried frailty phenotype & individual components



Roshanravan et al, ***AJKD*** 2012.

Fried frailty phenotype in ESKD patients on dialysis





- *Intermediate frailty & frailty associated with 2.6-2.7-fold higher mortality*
- *Frailty associated with 1.4-fold higher risk hospitalization*

McAdams-Demarco et al, ***JAGS*** 2013.

MALNUTRITION &
PROTEIN ENERGY WASTING

Malnutrition vs. Protein Energy Wasting (PEW)

MALNUTRITION

- **Induced by insufficient dietary intake**

PEW

- **Induced by ↑ body protein catabolism (not just ↓ diet)**
- **May or may not be corrected by ↑ dietary intake alone**

Fouque et al. ***KI 2008***.
Rhee, Molnar, Kovesdy. ***Ikizler & Mitch Handbook of Nutrition & the Kidney 2017.***

What is Protein Energy Wasting?

"Kidney Disease Wasting"
CKD & AKI

PEW is a condition of:
↓ body protein mass
↓energy/fuel reserves

"Cachexia"
Severe PEW

Biochemical abnormality

↓ Body mass

↓ Muscle mass

↓ Protein or energy intake

Fouque et al. ***KI*** 2008.
Rhee, Molnar, Kovesdy. ***Ikizler & Mitch Handbook of Nutrition & the Kidney*** 2017.

ISRNM criteria for diagnosis of PEW

BIOCHEMICAL
Albumin <3.8 g/dl
Pre-albumin <30 mg/dl*
Cholesterol <100 mg/dl

BODY MASS
BMI <23 kg/m^2
Unintentional ↓ weight:
5% in 3 months or
10% in 6 months
Body fat % <10%

ISRNM DIAGNOSTIC CRITERIA:
3 out of 4 categories

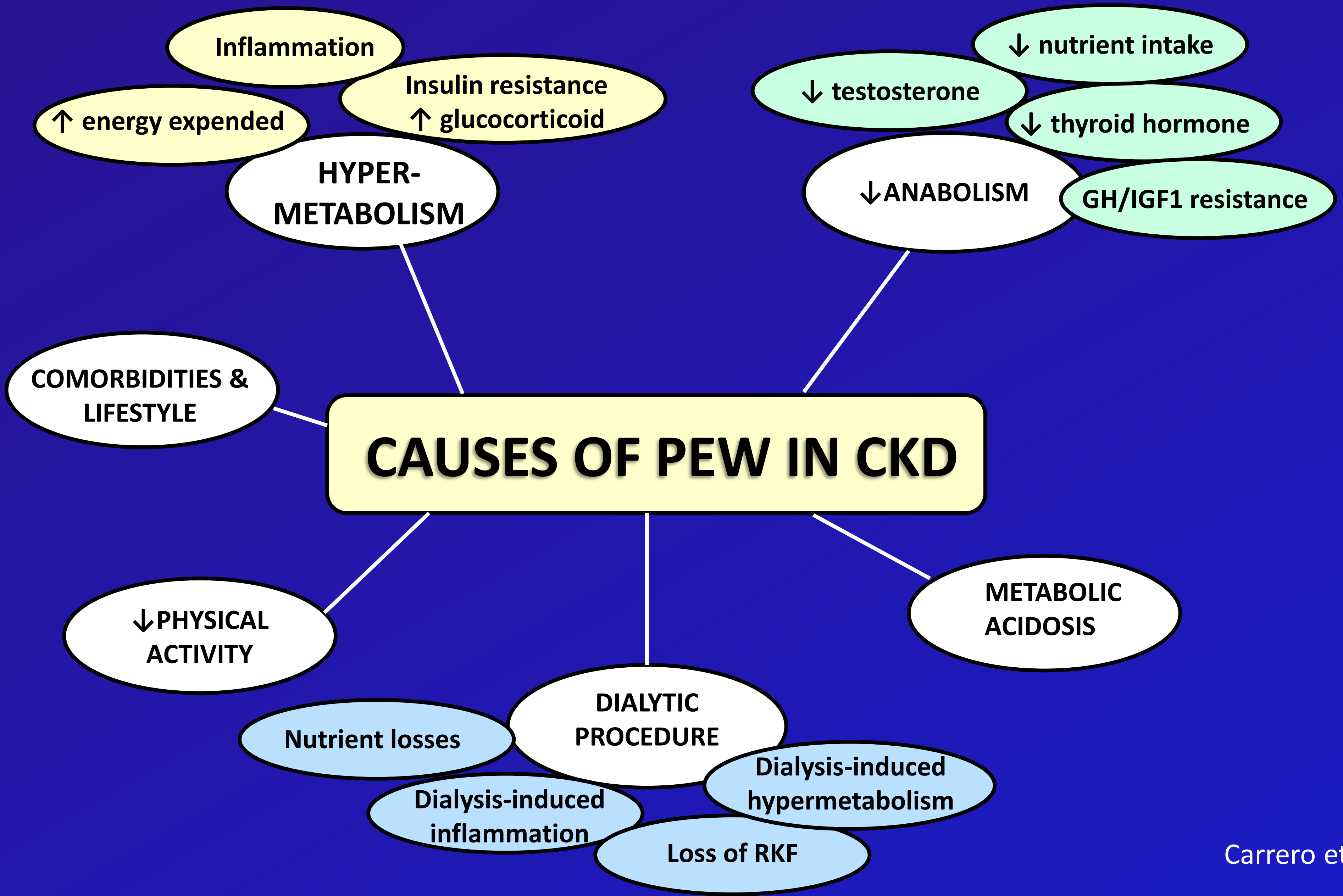
**For ESRD*

MUSCLE MASS
Muscle wasting:
5% in 3 months or
10% in 6 months
↓ MAMC
Cr appearance

DIETARY INTAKE
Unintentional ↓ DPI:
*<0.8 g/kg/day ≥2 mo's**
Unintentional ↓ DEI:
<25 kcal/kg/day ≥2 mo's

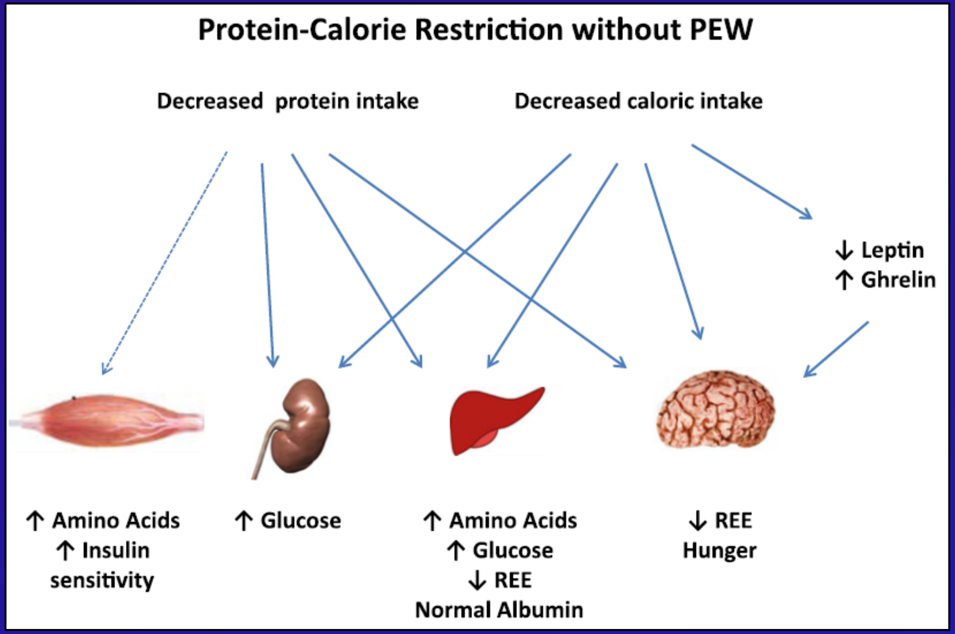
Fouque et al. ***KI*** 2008.
Rhee, Molnar, Kovesdy. ***Ikizler & Mitch Handbook of Nutrition & the Kidney*** 2017.

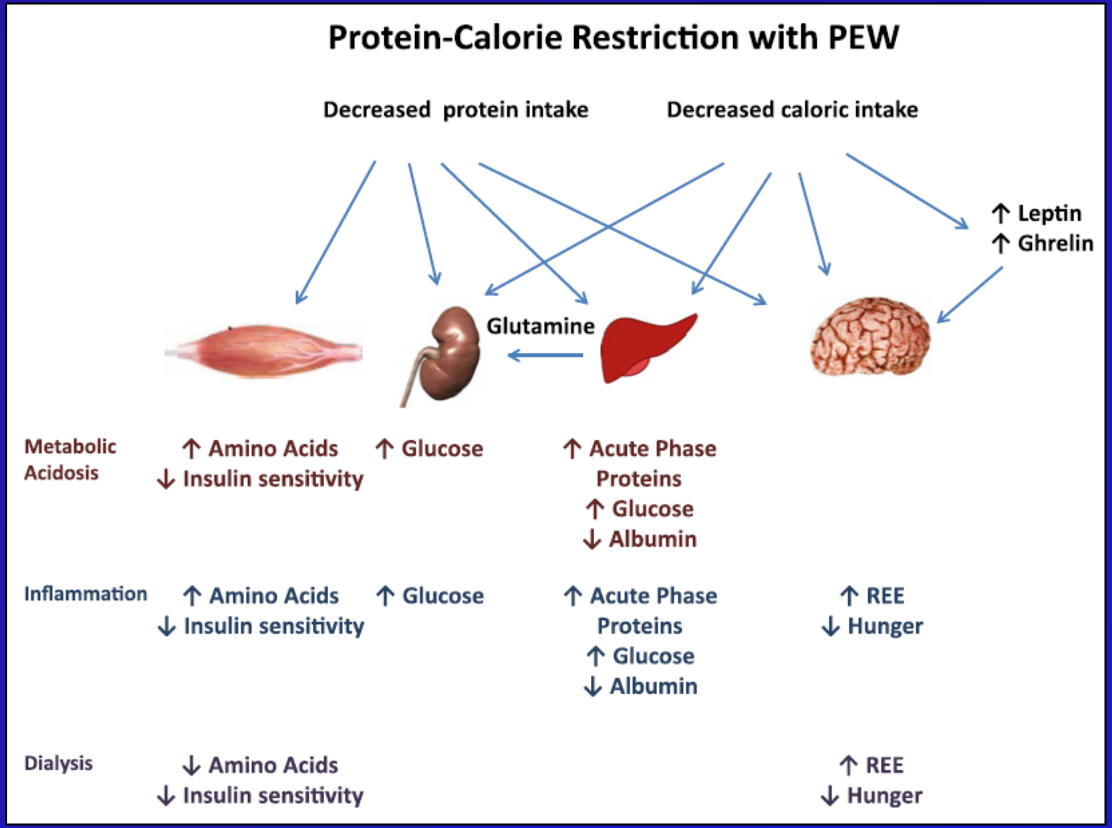
Multifactorial causes of PEW & malnutrition



Carrero et al. *JReN* 2013.

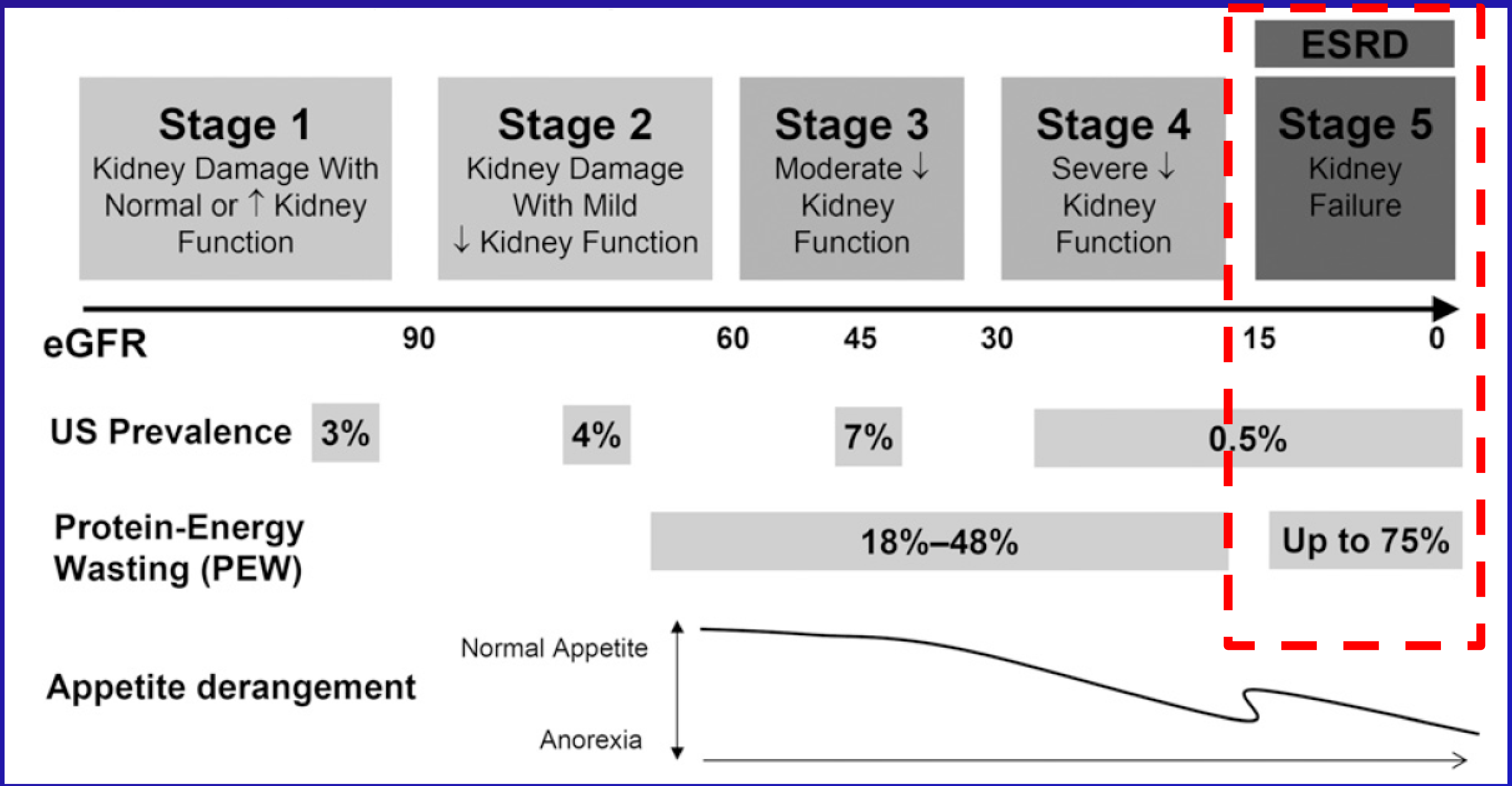
Maladaptive response to
↓ protein & energy intake in PEW





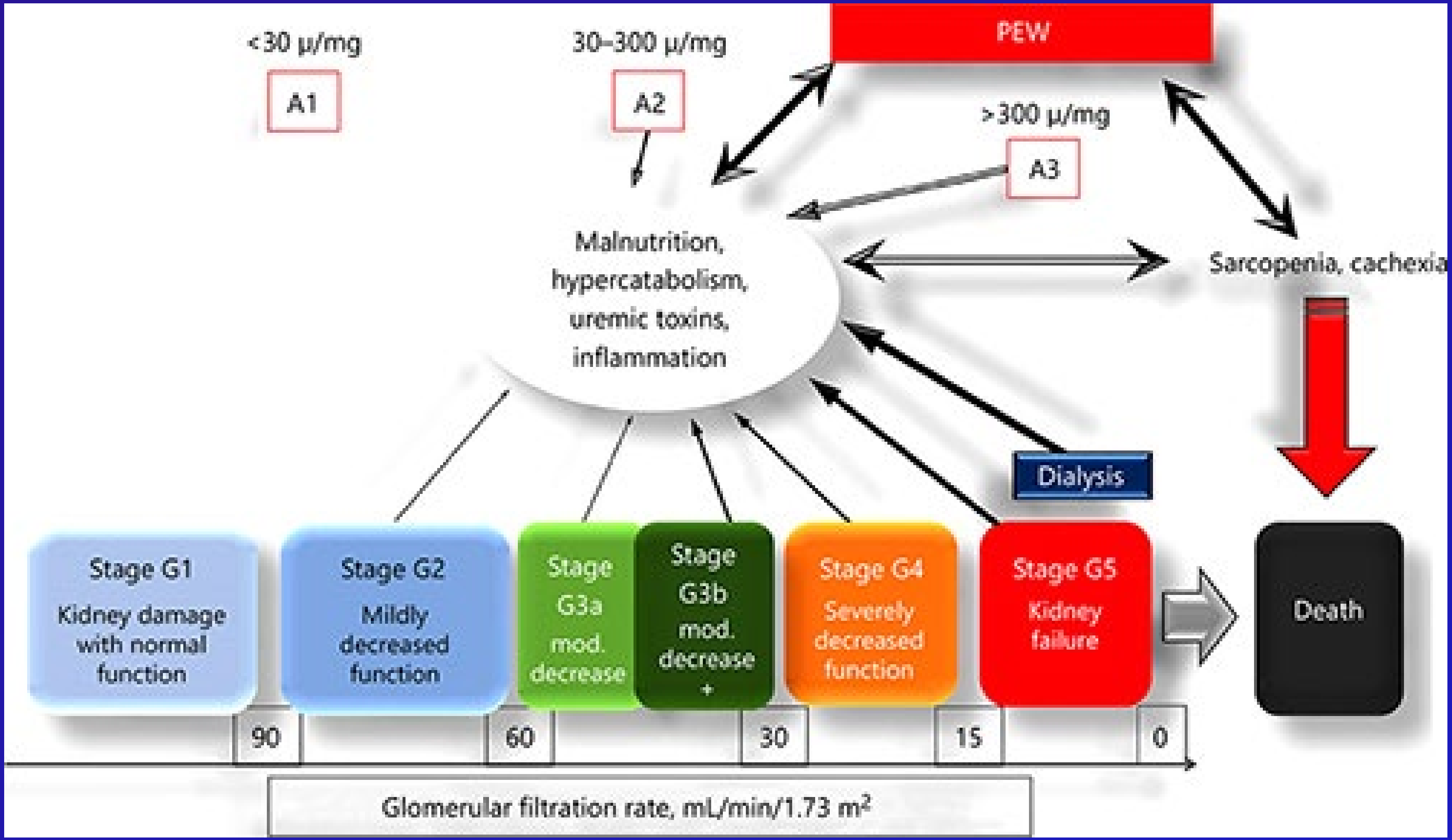
Carrero et al. *JReN* 2013.

↑ Prevalence of PEW with CKD → ESKD



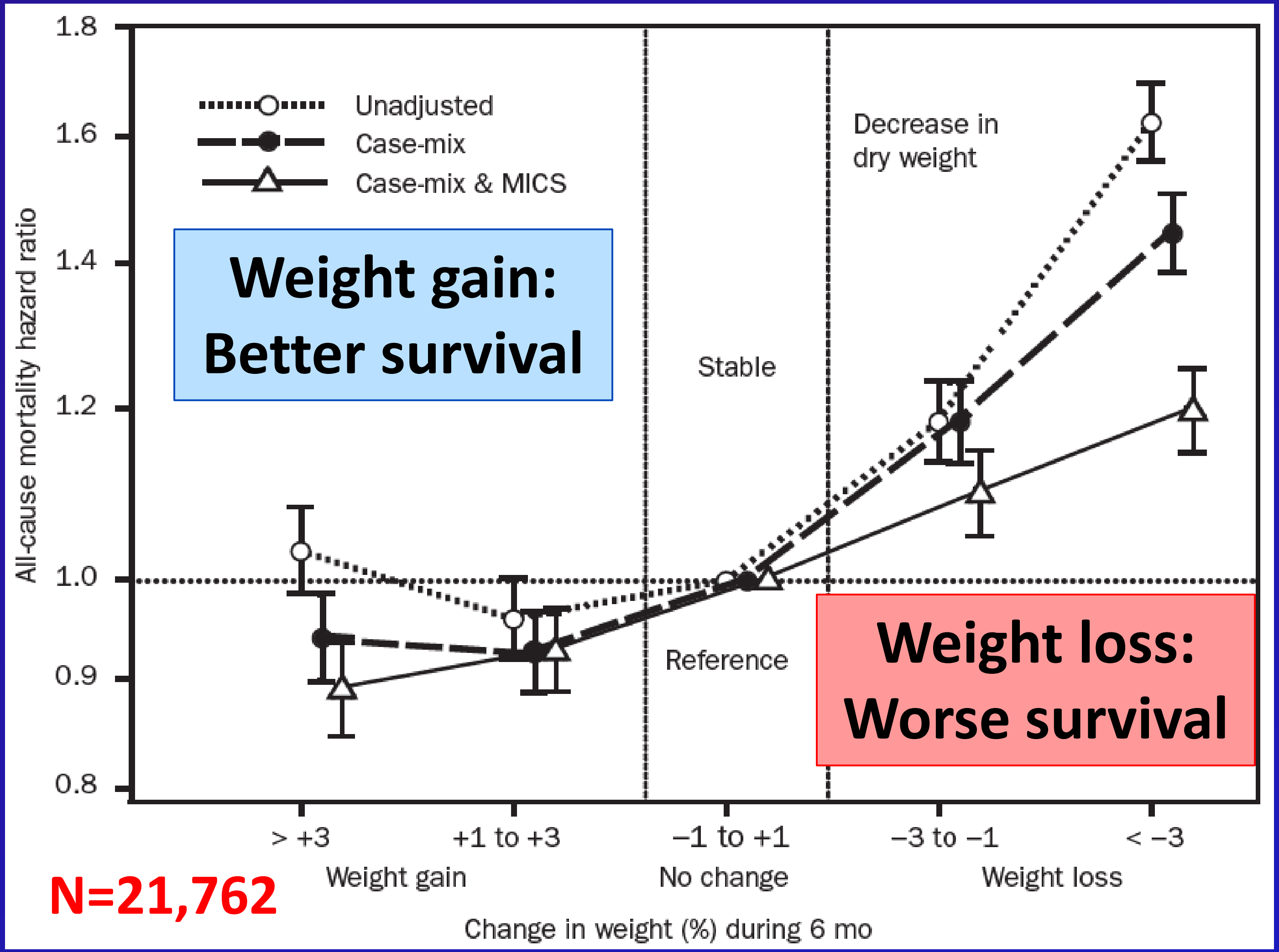
Kovesdy et al. ***AJCN*** 2013.

PEW & cachexia are associated with morbidity & mortality in CKD



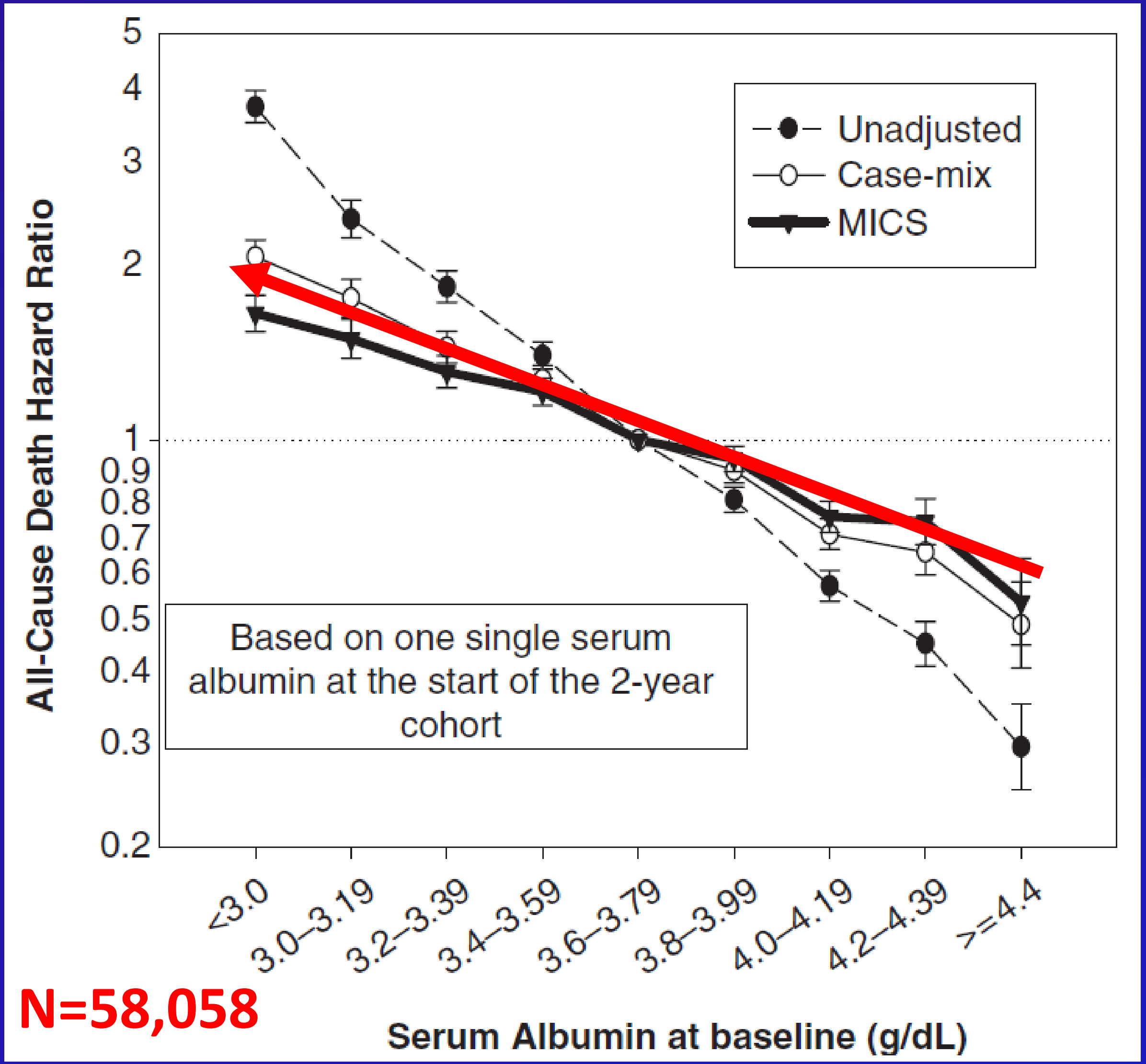
Hanna, Ghobry, Wassef, Rhee, Kalantar, ***Blood Purif*** 2020.

↓ Weight associated with ↑ mortality in HD



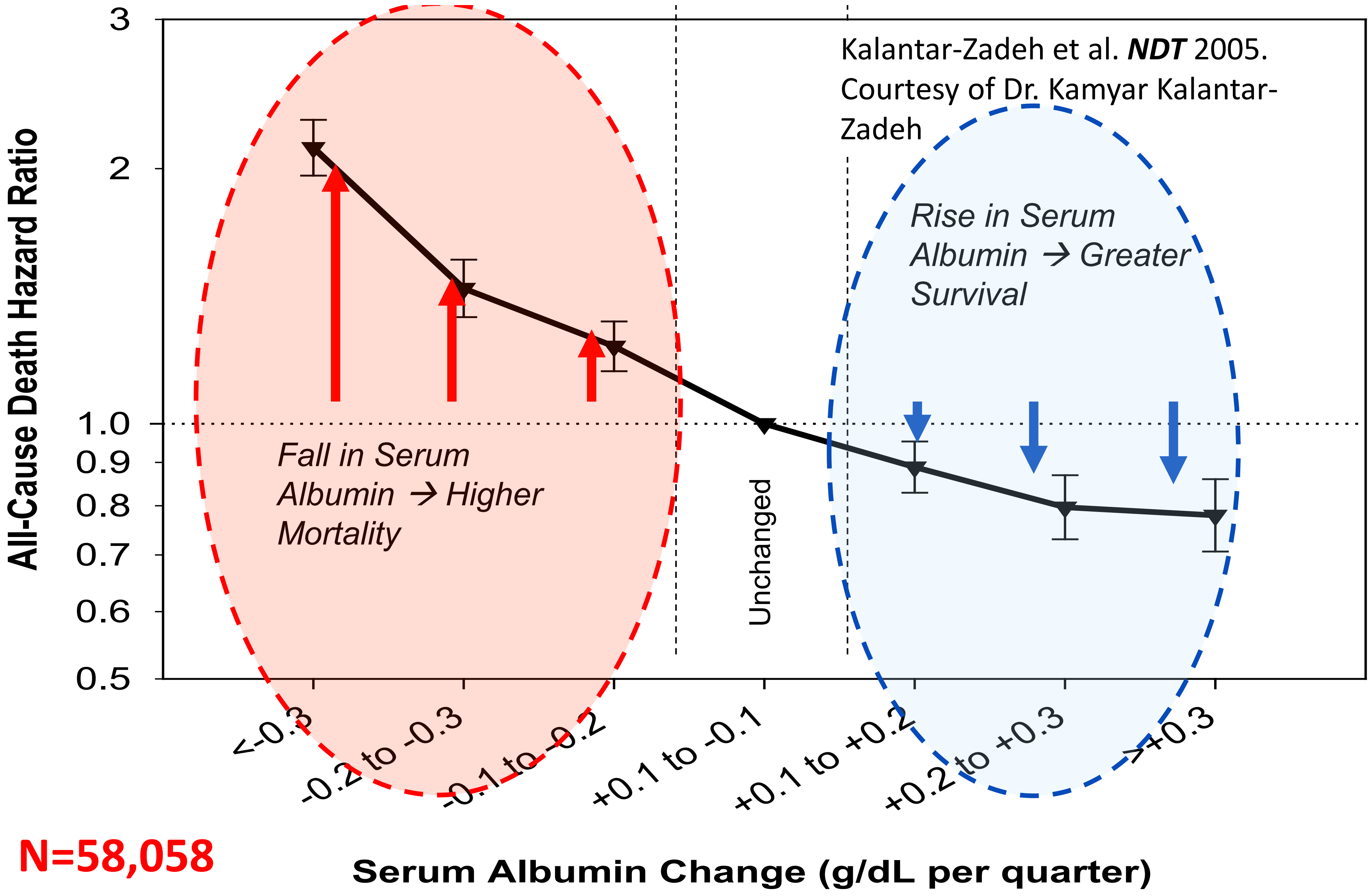
Kalantar-Zadeh et al. ***Mayo Clin Proceedings*** 2010.

Lower serum albumin associated with ↑ mortality in HD



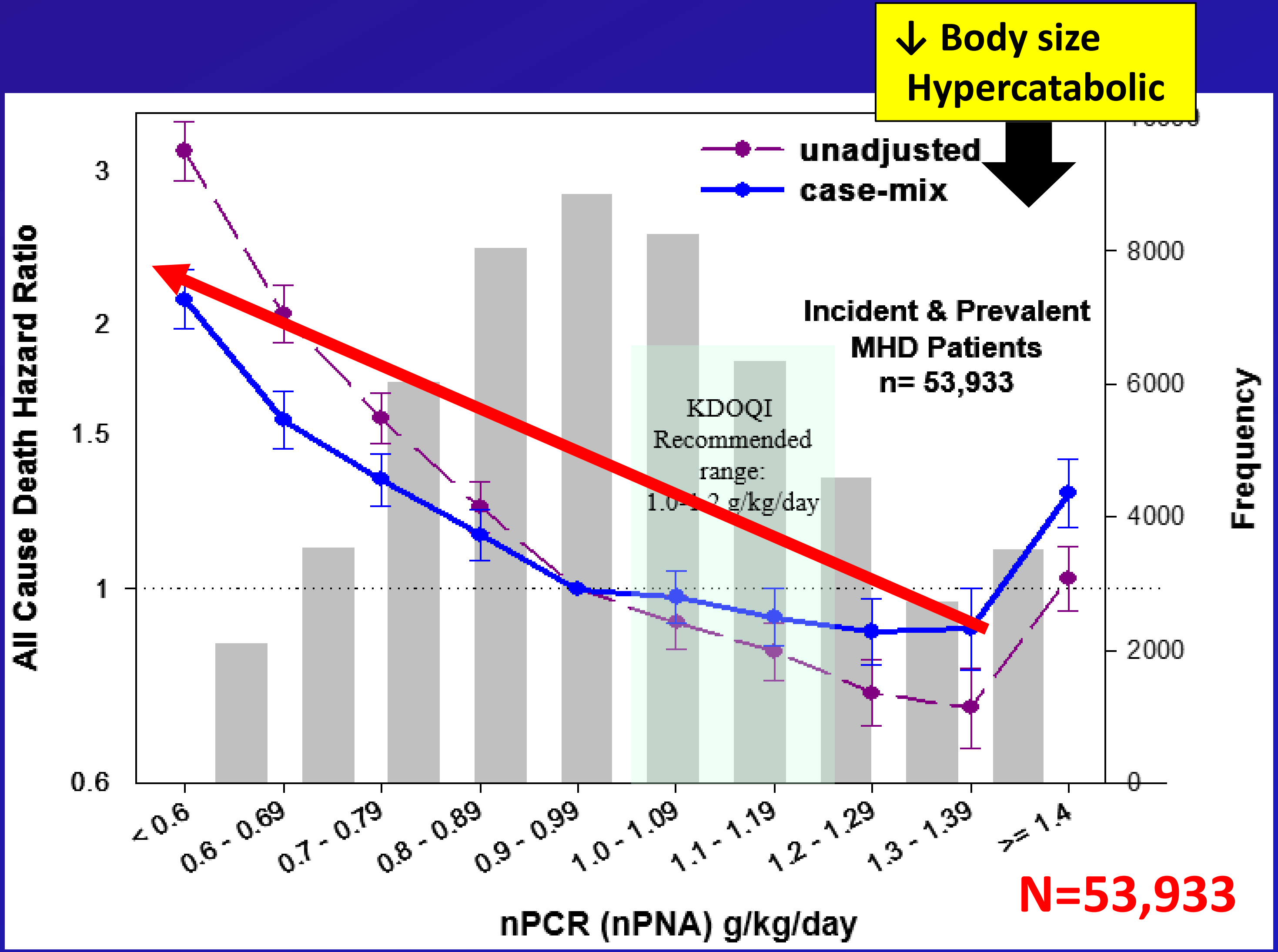
Kalantar-Zadeh et al. ***NDT*** 2005.

Higher serum albumin associated with ↓ mortality in HD



N=58,058

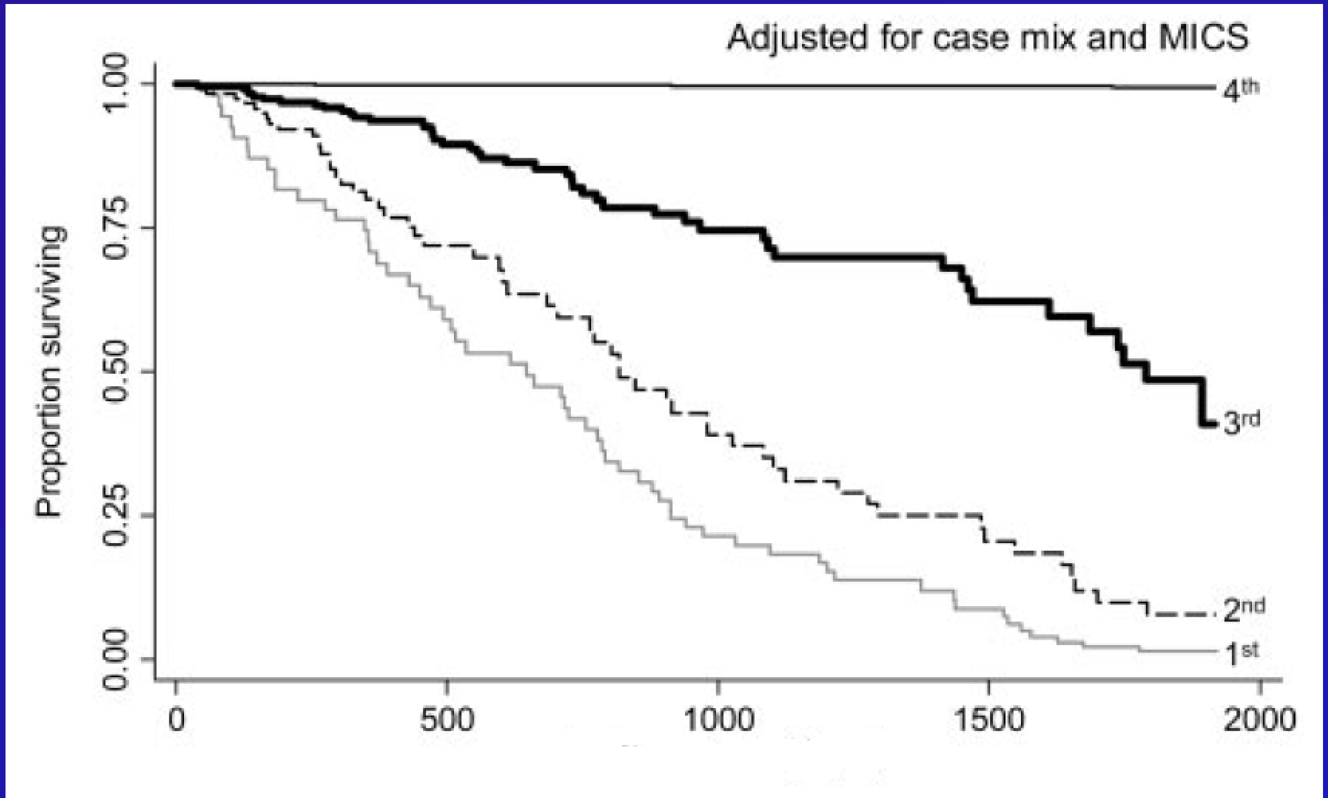
Low & very high nPCR associated with ↑ death in HD



Shinaberger et al. ***AJKD*** 2006.
Ravel et al. ***Jl Nut*** 2013.

Greater skeletal mass associated with ↑ survival in HD

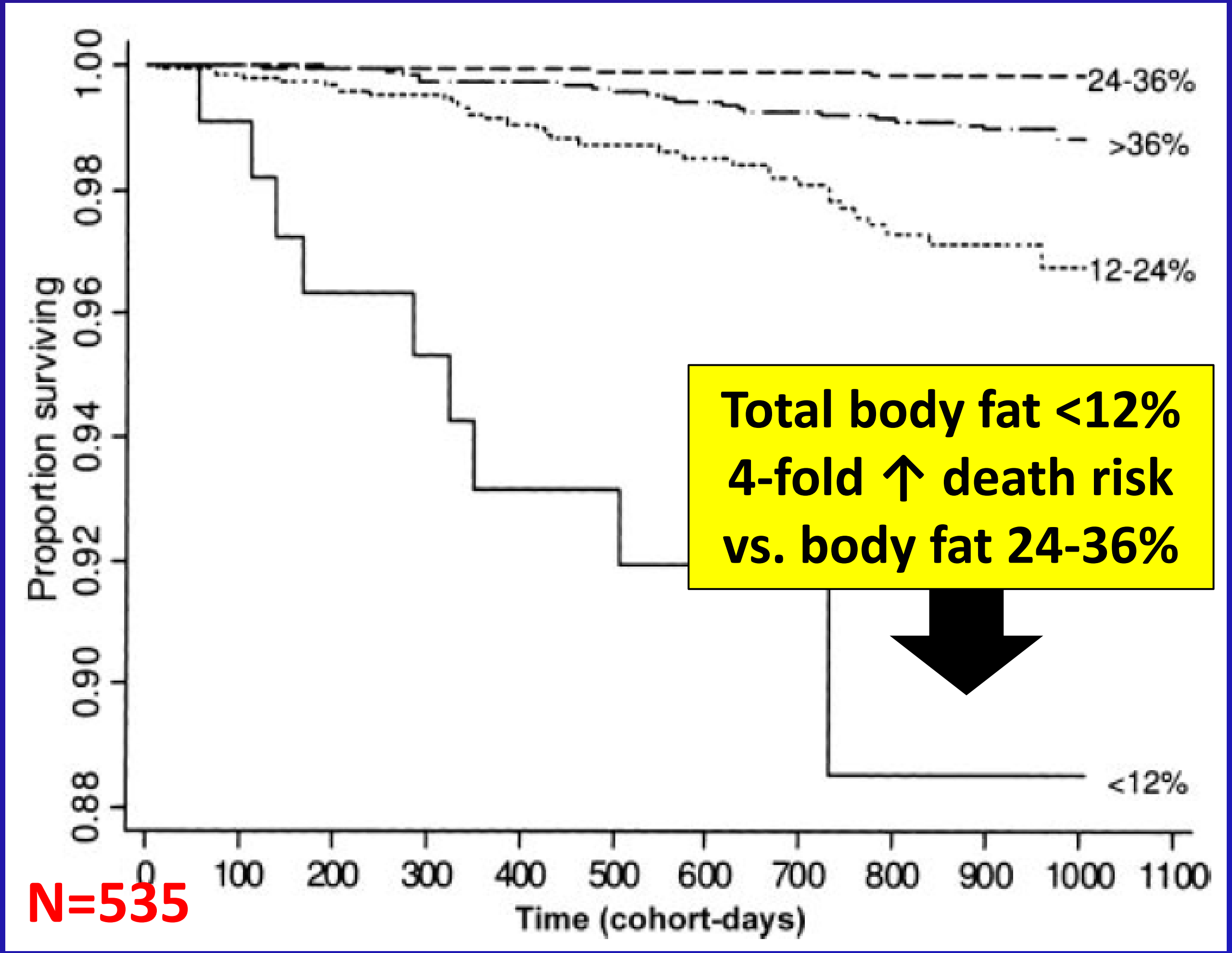
MAMC (cm) = mid-arm circumference (cm) 3.142 TSF (cm)



N=792

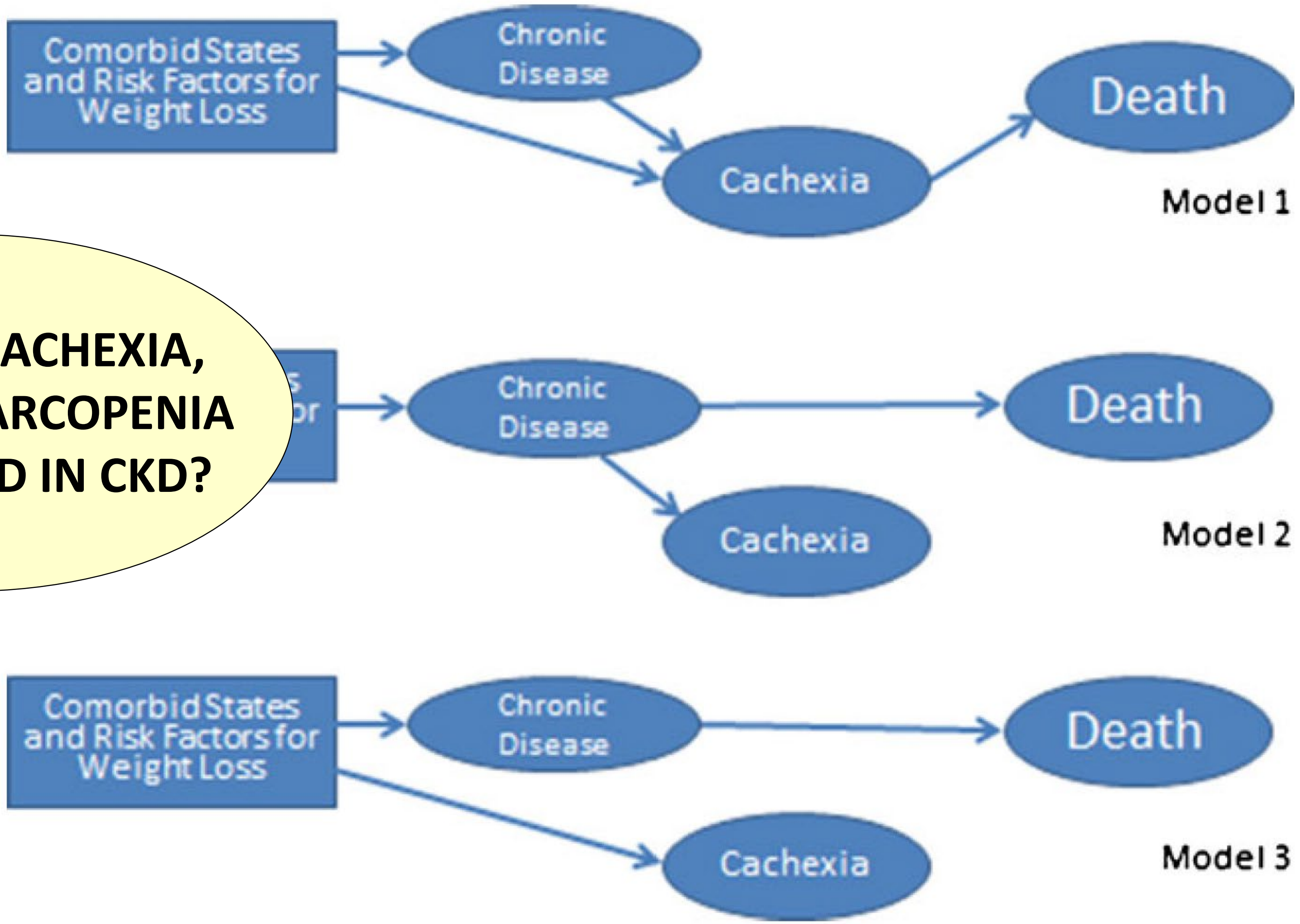
Noori et al. ***CJASN*** 2010.

Greater body fat associated with ↑ survival in HD



Kalantar-Zadeh et al. ***AJCN*** 2006.

Potential causal models of PEW/cachexia and death



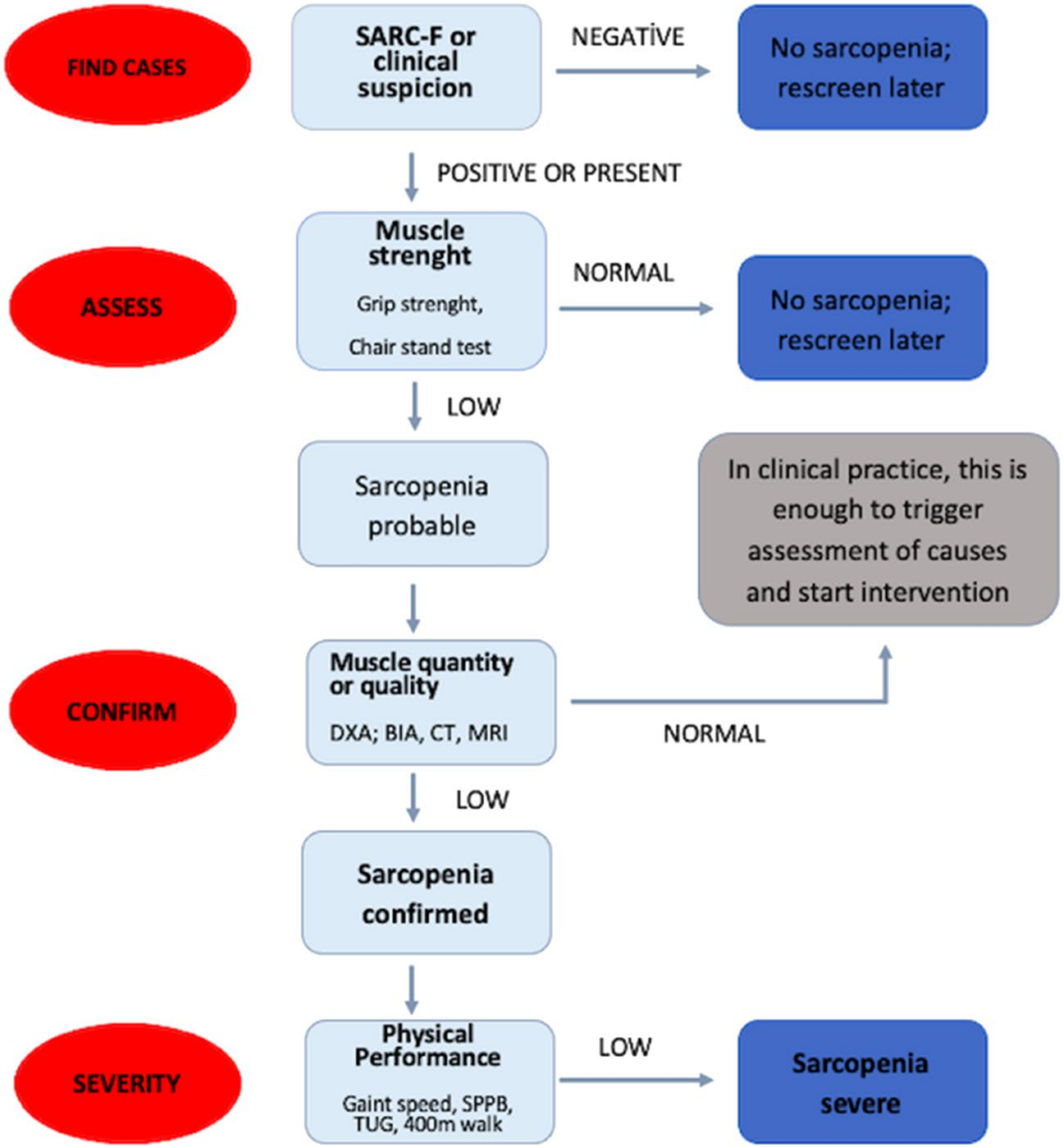
CAN PEW/CACHEXIA, FRAILTY, & SARCOPENIA BE REVERSED IN CKD?

Kalantar, Rhee…Kovesdy, ***JCSM*** 2013.

SCREENING TOOLS & EARLY DETECTION

SARCOPENIA

European Working Group on Sarcopenia in Older People (2018) Algorithm



Gungor, Ulu, Hasbal, Anker, Kalantar. ***JCSM*** 2021.

SARC-F: Simple 5-item survey

SARCOPENIA

Component	Question	Scoring			Score
		0	1	2	
Strength	How much difficulty do you have in lifting and carrying 10 pounds?	None	Some	A lot or unable	
Assistance in walking	How much difficulty do you have walking across a room?	None	Some	A lot, use aids, or unable	
Rise from a chair	How much difficulty do you have transferring from a chair or bed?	None	Some	A lot or unable without help	
Climb stairs	How much difficulty do you have climbing a flight of 10 stairs?	None	Some	A lot or unable	
Falls	How many times have you fallen in the past year?	None	1-3 falls	4 or more falls	
				Total score:	

A total score of equal to or greater than 4 is predictive of sarcopenia and poor outcomes.

Other potential frailty screening tools

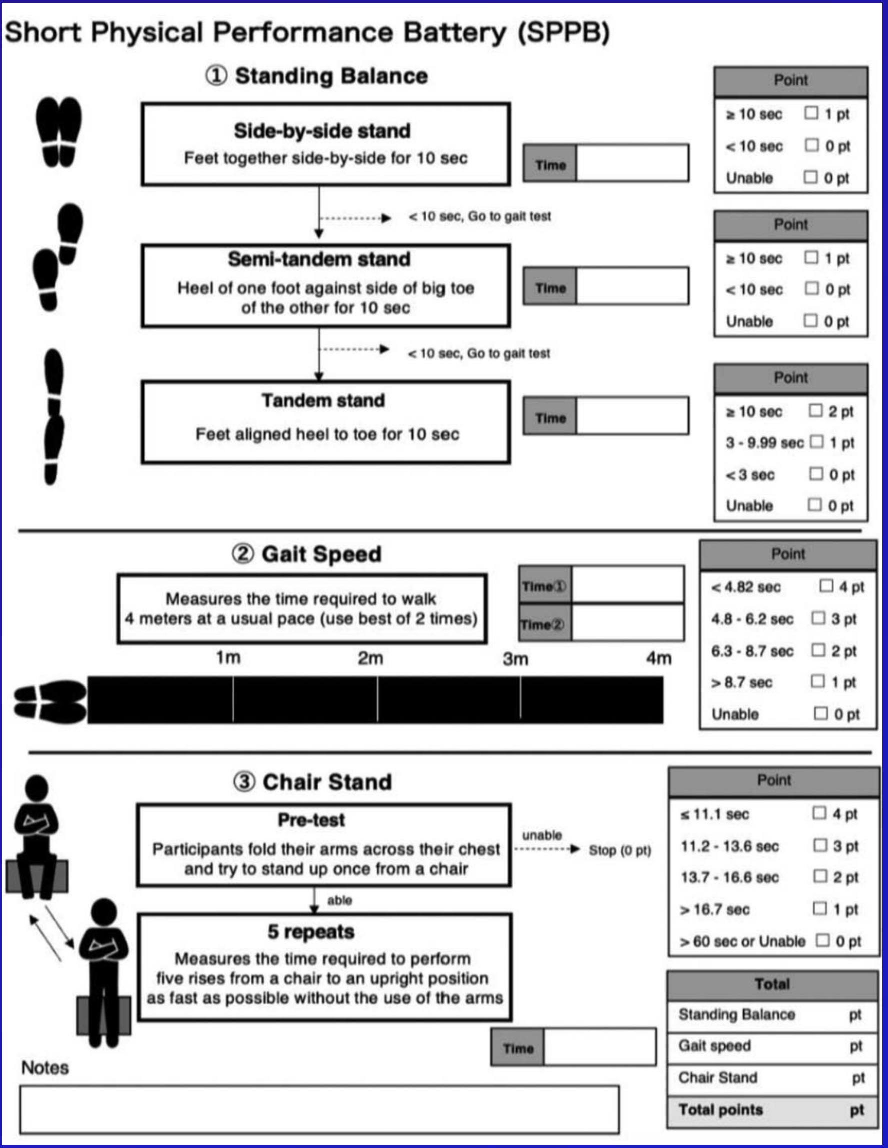
FRAILTY

Method of Assessment	Validated in CKD?	Strengths as a Screening Tool	Limitations as a Screening Tool
Fried phenotype	Yes	Objective Concise Robust data in CKD	Does not provide a graded measure of frailty Potentially cumbersome
Short Physical Performance Battery	Yes	Objective Semi-quantitative	Only based on physical examination Potentially cumbersome
Frailty index	Yes	Customizable Semi-quantitative	May require thresholds to be pragmatic Potentially cumbersome
Groningen frailty indicator	Yes	Ease of use Semi-quantitative	Limited sensitivity May miss some deficits
Multidisciplinary prognostic index	Yes	Objective Good prognostic validity	May not be generalizable to outpatients Potentially cumbersome
Clinical frailty scale	Yes	Ease of use Semi-quantitative	Subjective Ideally requires knowledge of the patient's baseline state Focuses primarily on function

Worthen, Tennankore. ***Intl Jl Neph Renovasc Disease*** 2019.

Short Physical Performance Battery (SPPB)

- SPPB predictive of mortality, hospitalization, and disability in elderly patients
  - ➢ Validated in CKD studies.
- Asseses 1) gait speed, 2) balance, and 3) chair stands
  - ➢ Each component ranges from 0-4
  - ➢ Total score ranges 0-12
  - ➢ Higher score indicates better performance)



Short Physical Performance Battery (SPPB)

① Standing Balance

Side-by-side stand
Feet together side-by-side for 10 sec
Time

Point	
≥ 10 sec	☐ 1 pt
< 10 sec	☐ 0 pt
Unable	☐ 0 pt

< 10 sec, Go to gait test

Semi-tandem stand
Heel of one foot against side of big toe of the other for 10 sec
Time

Point	
≥ 10 sec	☐ 1 pt
< 10 sec	☐ 0 pt
Unable	☐ 0 pt

< 10 sec, Go to gait test

Tandem stand
Feet aligned heel to toe for 10 sec
Time

Point	
≥ 10 sec	☐ 2 pt
3 - 9.99 sec	☐ 1 pt
< 3 sec	☐ 0 pt
Unable	☐ 0 pt

② Gait Speed

Measures the time required to walk 4 meters at a usual pace (use best of 2 times)
Time①
Time②
1m 2m 3m 4m

Point	
< 4.82 sec	☐ 4 pt
4.8 - 6.2 sec	☐ 3 pt
6.3 - 8.7 sec	☐ 2 pt
> 8.7 sec	☐ 1 pt
Unable	☐ 0 pt

③ Chair Stand

Pre-test
Participants fold their arms across their chest and try to stand up once from a chair
unable → Stop (0 pt)
able

5 repeats
Measures the time required to perform five rises from a chair to an upright position as fast as possible without the use of the arms
Time

Point	
≤ 11.1 sec	☐ 4 pt
11.2 - 13.6 sec	☐ 3 pt
13.7 - 16.6 sec	☐ 2 pt
> 16.7 sec	☐ 1 pt
> 60 sec or Unable	☐ 0 pt

Total	
Standing Balance	pt
Gait speed	pt
Chair Stand	pt
Total points	**pt**

Notes

Otobe, Rhee…Kopple. ***Curr Opin Neph HTN*** 2022.

"Malnutrition Inflammation Score" (MIS)

PEW

SUBJECTIVE GLOBAL ASSESSMENT

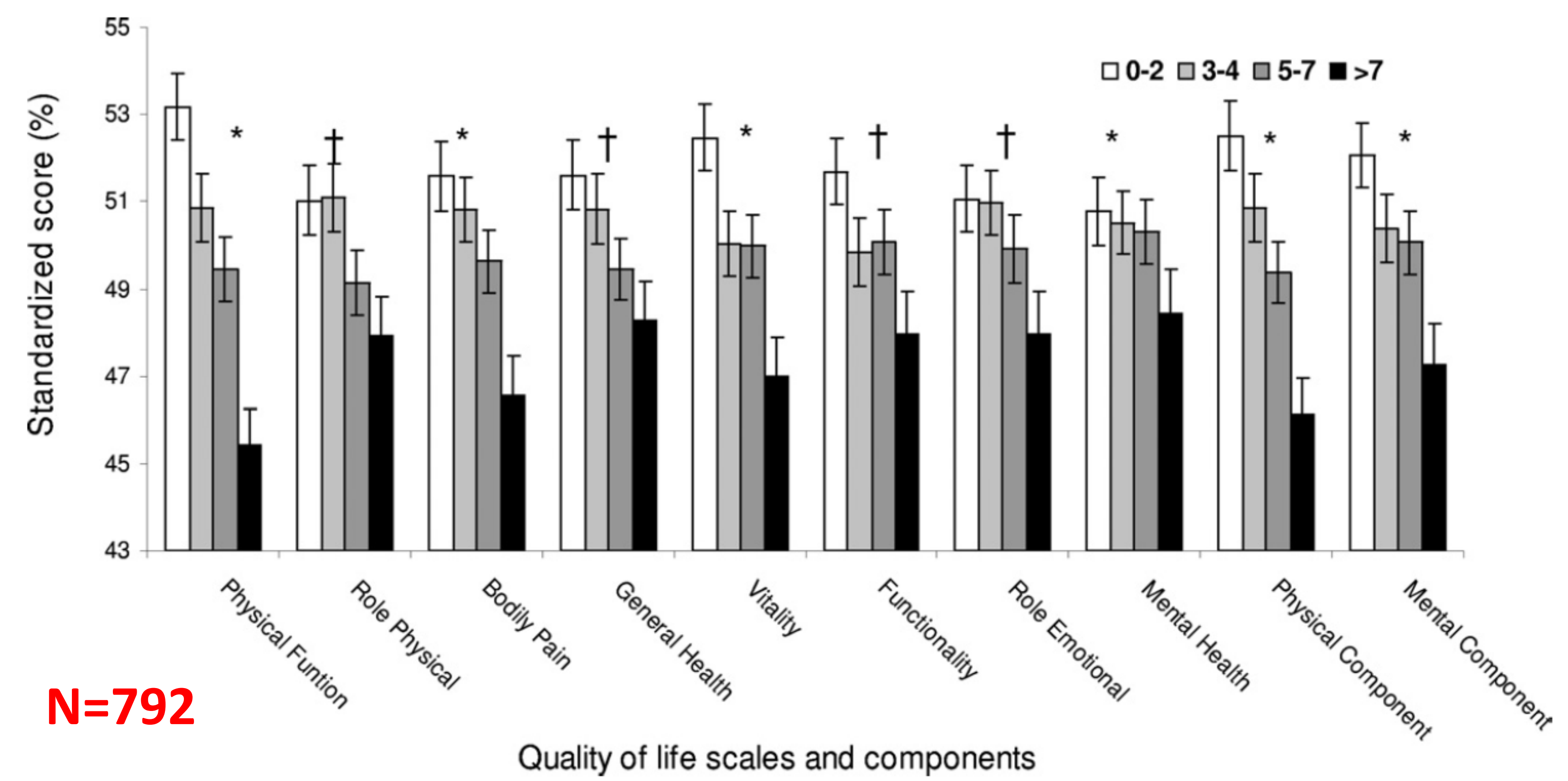
BMI

LAB TESTS

MIS Components	Score 0	1	2	3
(A) Medical history:				
1. Change in end dialysis dry weight (overall change in the past 3-6 mo)	<0.5 kg	0.5-1.0kg	≥1 kg but <5%	≥5%
2. Dietary intake	Good appetite, no deterioration in dietary intake	Suboptimal solid dietary intake	Moderate overall decrease to full liquid diet	Hypocaloric liquid to starvation
3. Gastrointestinal symptoms	No symptoms with good appetite	Mild symptoms, poor appetite, or nauseated occasionally	Occasional vomiting or moderate GI symptoms	Frequent diarrhea or vomiting or severe anorexia
4. Functional capacity (nutritionally related functional impairment)	Normal to improved functional capacity, feeling fine	Occasional difficulty with baseline ambulation or feeling tired frequently	Difficulty with otherwise independent activities (eg, going to bathroom)	Bed/chair-ridden or little to no physical activity
5. Comorbidity*	No comorbidity	Mild comorbidity (excluding MCC†)	Moderate comorbidity (including 1 MCC*)	Any severe multiple comorbidity (≥2 MCCs*)
(B) Physical examination				
6. Decreased fat stores or loss of subcutaneous fat (below eyes, triceps, biceps, triceps, chest)	No change	Mild	Moderate	Severe
7. Signs of muscle wasting (temple, clavicle, scapula, ribs, quadriceps, knee, interosseous)	No change	Mild	Moderate	Severe
(C) Body size				
8. Body mass index (kg/m^2)	≥20	18-19.9	16-17.99	<16
(D) Laboratory parameters				
9. Serum albumin (g/L)	≥4	3.5-3.9	3.0-3.4	<3.0
10. Serum total iron-binding capacity (mg/dL)	≥250	200-249	150-199	<150

Rambod et al. ***AJKD*** *2009.*

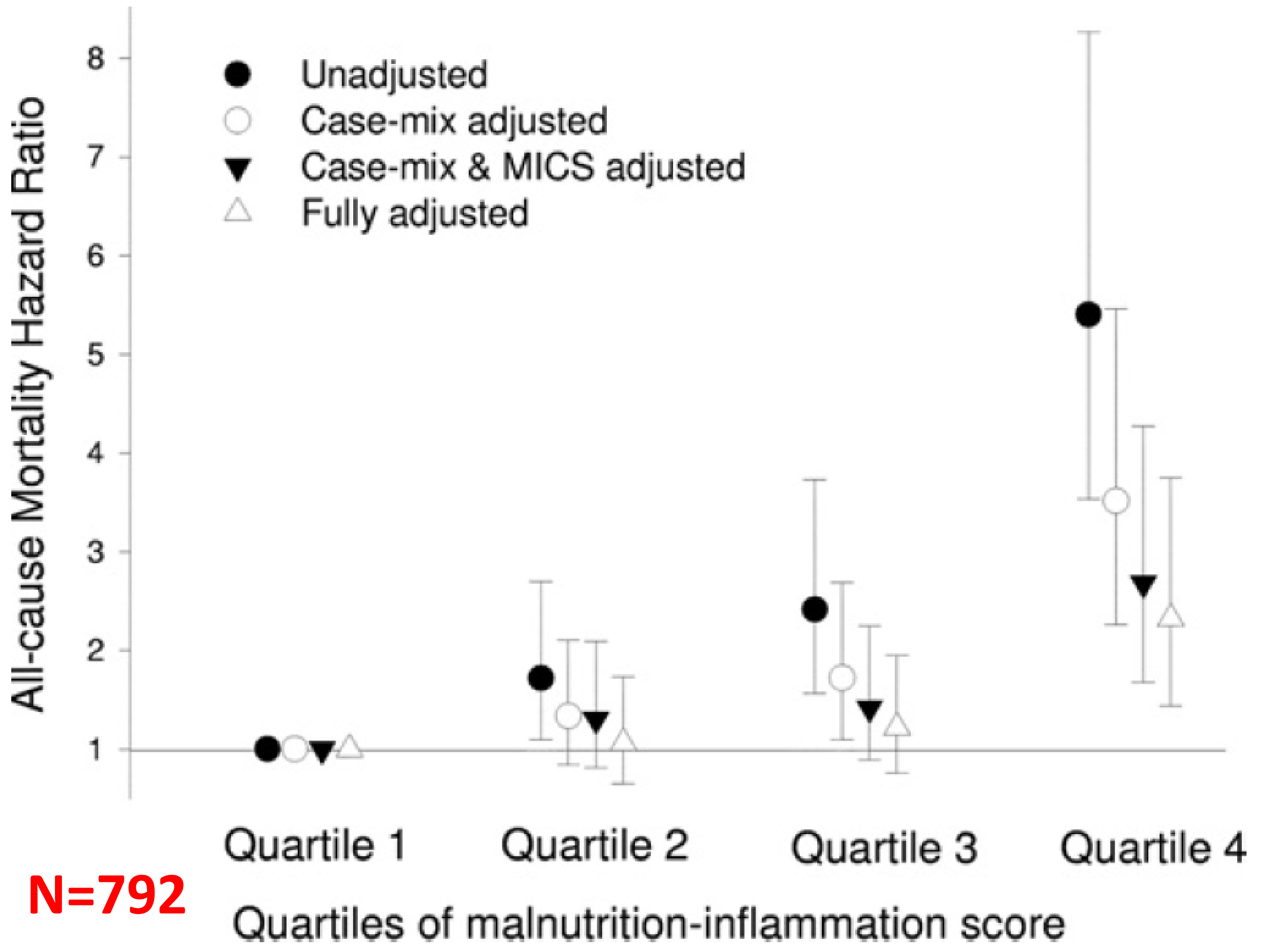
↑ Malnutrition Inflammation Score & ↓ HRQOL in HD



Rambod et al. ***AJKD*** *2009.*

PEW

↑ Malnutrition Inflammation Score & ↑ mortality in HD

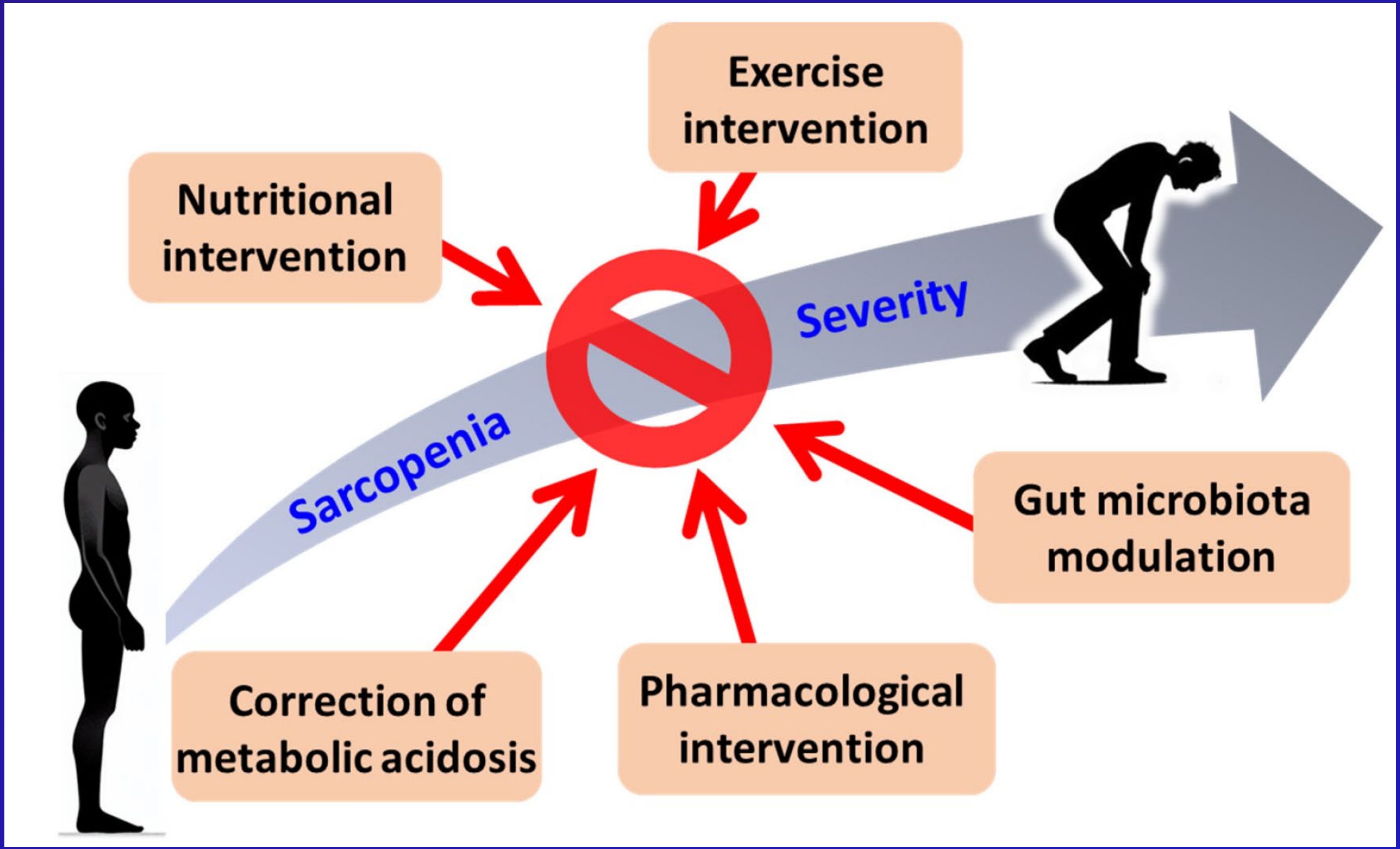


N=792

Rambod et al. ***AJKD*** *2009.*

TREATMENT APPROACHES

Multi-faceted treatment of sarcopenia, frailty, & PEW



Tsai et al. ***Biomedicines*** 2025.

Multi-faceted management approaches

NUTRITIONAL SUPPORT

- Oral nutrional supplement
- IDPN
- TPN

Avoid excess restriction

Meals w/ dialysis

EXERCISE

- Interventions that increase physical activity

PHARMACO-THERAPIES

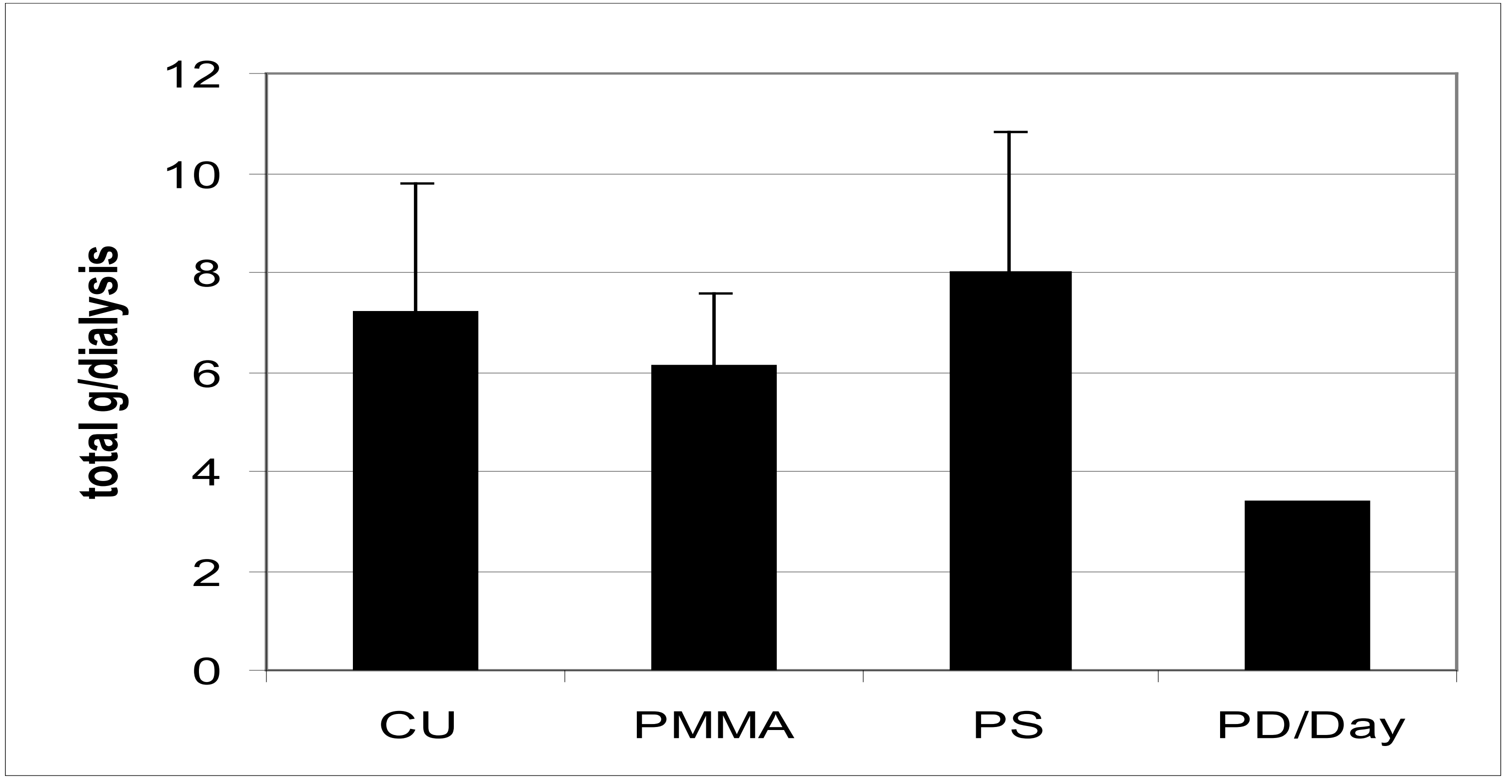
- Vitamin D
- Oral alkali
- Testosterone

Dialysis patients are in negative nitrogen balance during HD

↓ Dietary intake + HD-associated catabolism

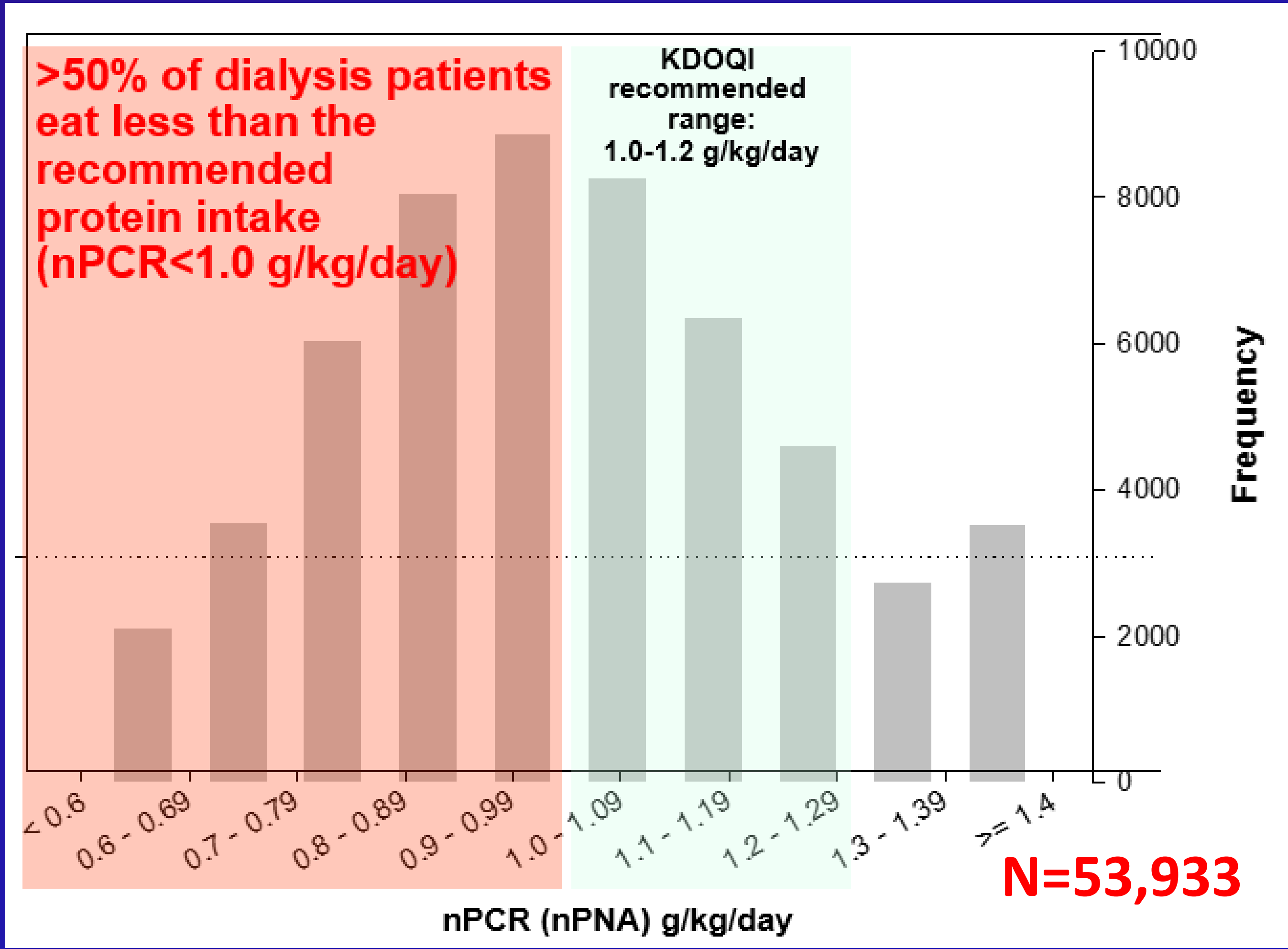
Inflammation + Insulin resistance +

Significant LOSS of Amino Acids into Dialysate



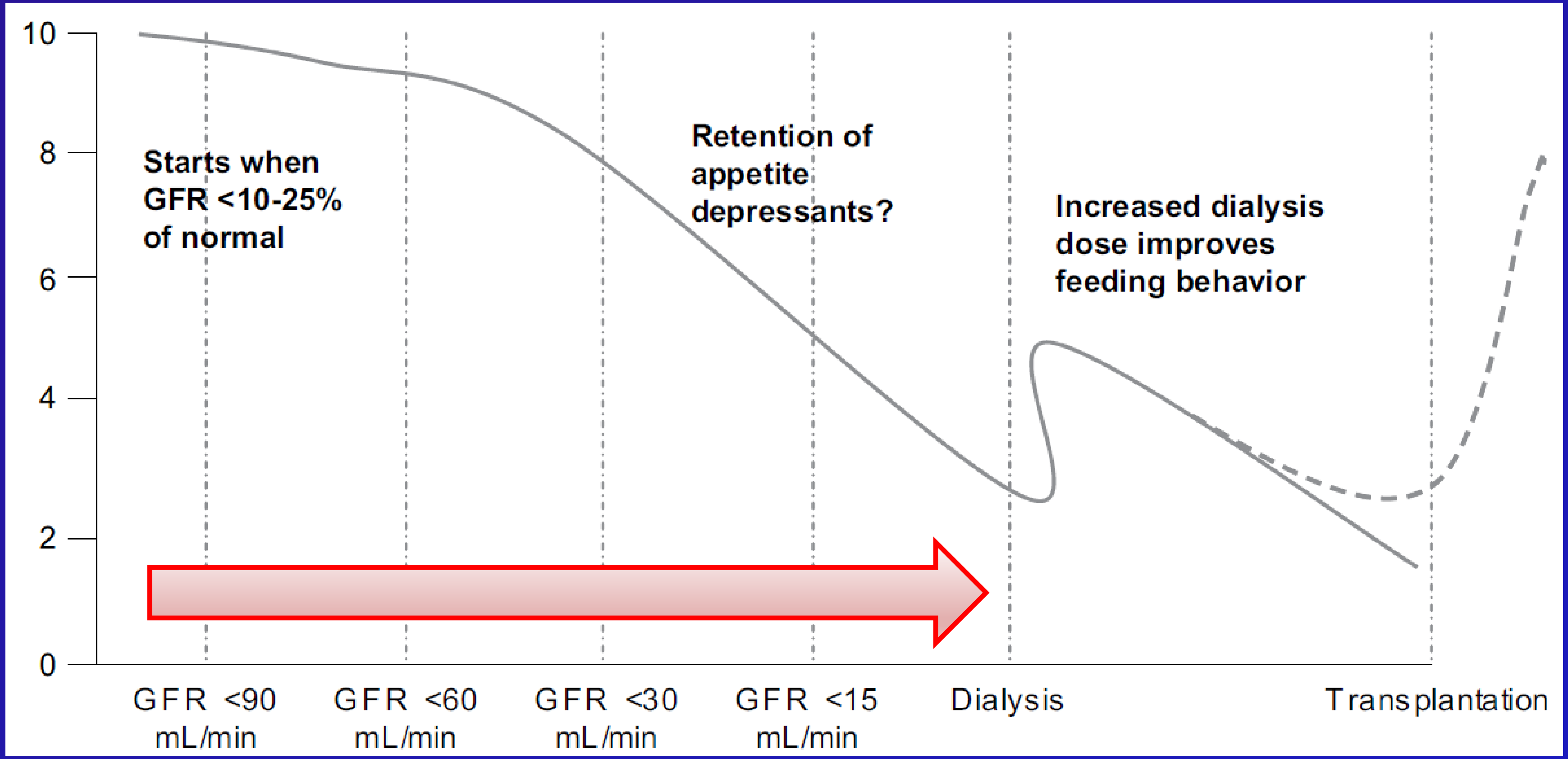
Ikizler, Hakim. ***KI*** 1994.
Courtesy of Dr. Kamyar Kalantar-Zadeh.

Low dietary protein intake is common in HD



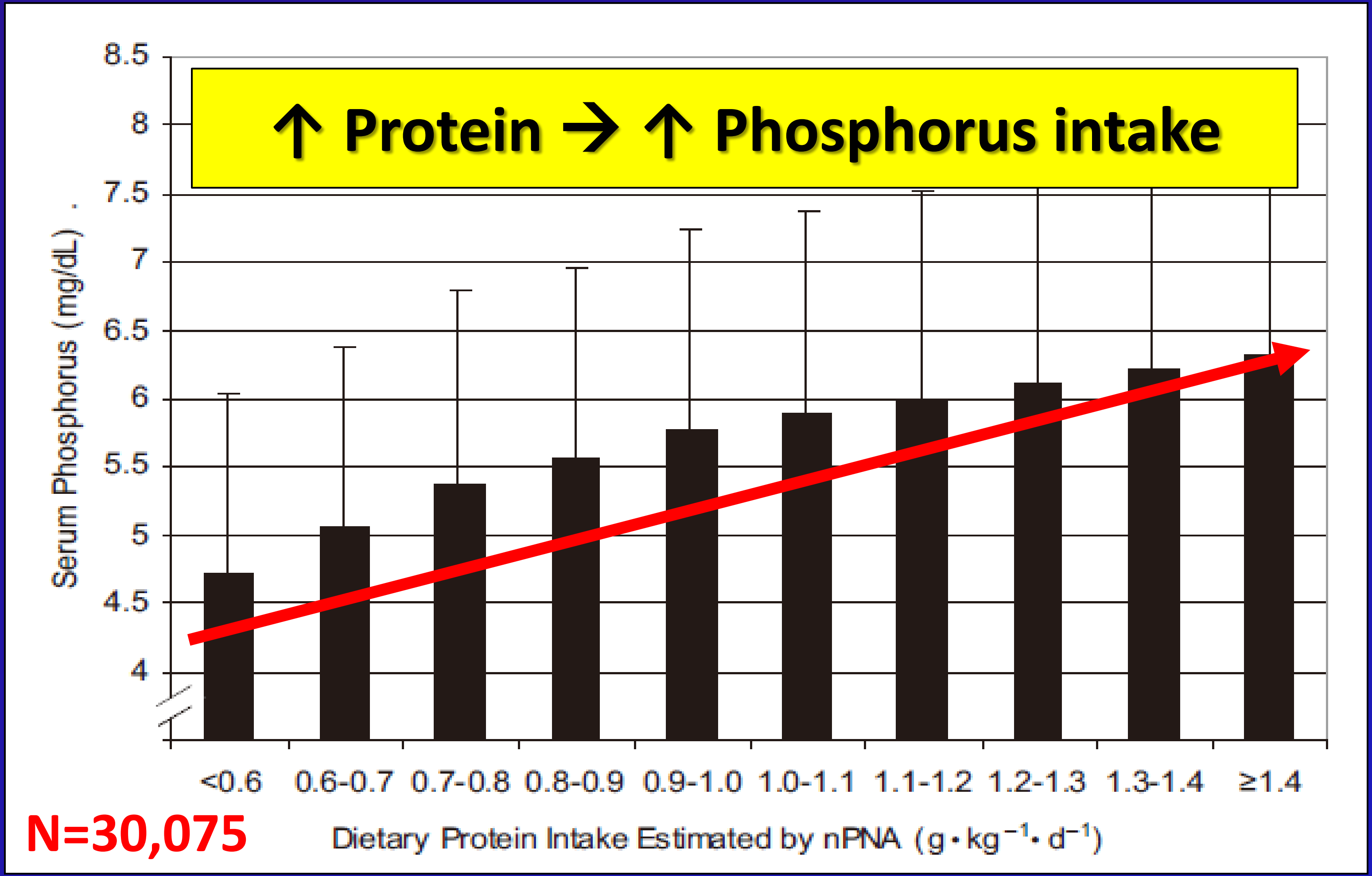
Shinaberger et al. ***AJKD*** 2006.

Loss of appetite with CKD progression



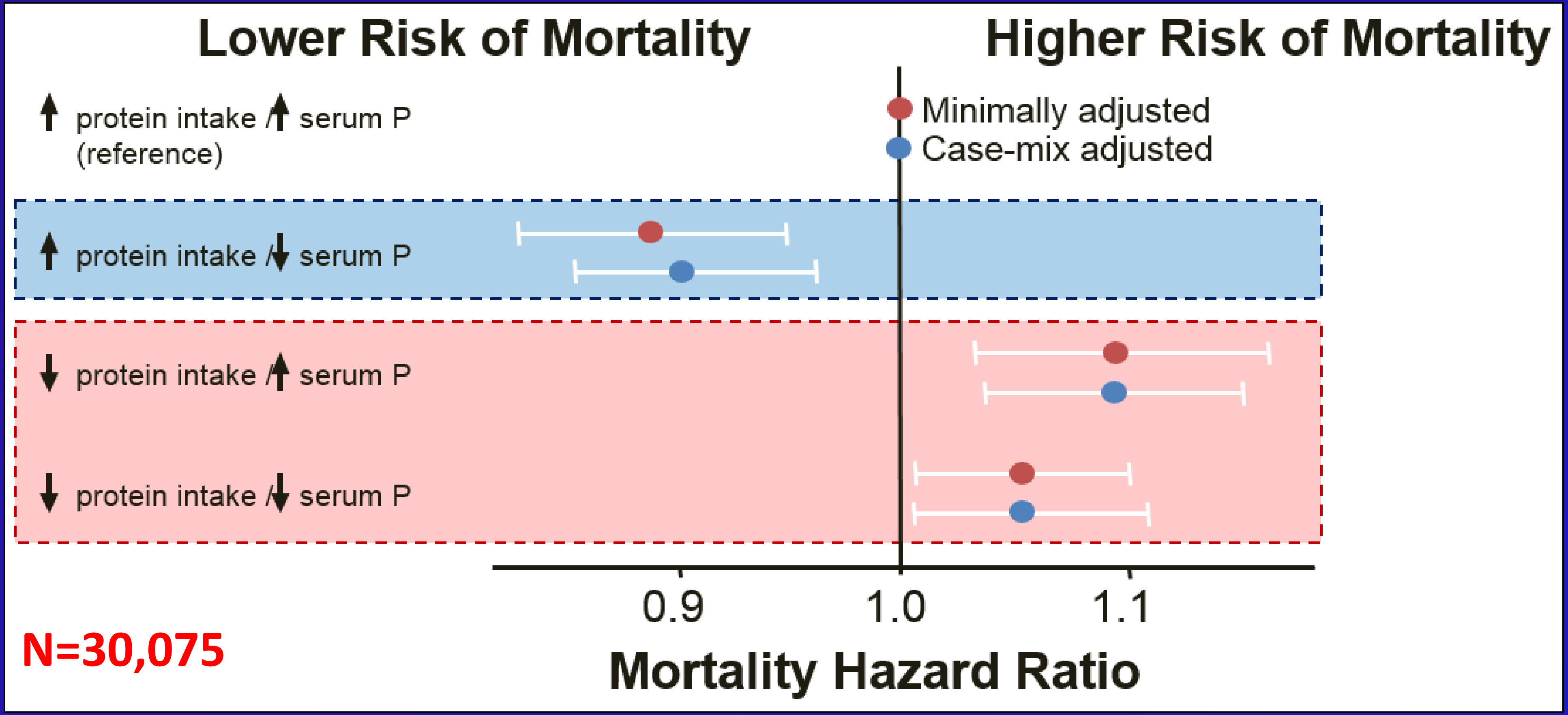
Carrero et al. ***JReN*** 2009.

Dietary protein & phosphorus intake closely correlated



Shinaberger…Kalantar-Zadeh, ***AJCN*** 2008.

Risk of restricting phosphorus intake by protein restriction may outweigh the benefit



Shinaberger…Kalantar-Zadeh, ***AJCN*** 2008.

Avoid excessive dietary restriction

REVIEW ARTICLE

CPE **Let Them Eat During Dialys… Opportunity to Improve Outco… Hemodialysis Patients**

Kamyar Kalantar-Zadeh, MD, MPH, PhD,,† and T. Alp …*

Seminars in Dialysis

VIEWS, VISIONS AND VISTAS IN DIALYSIS

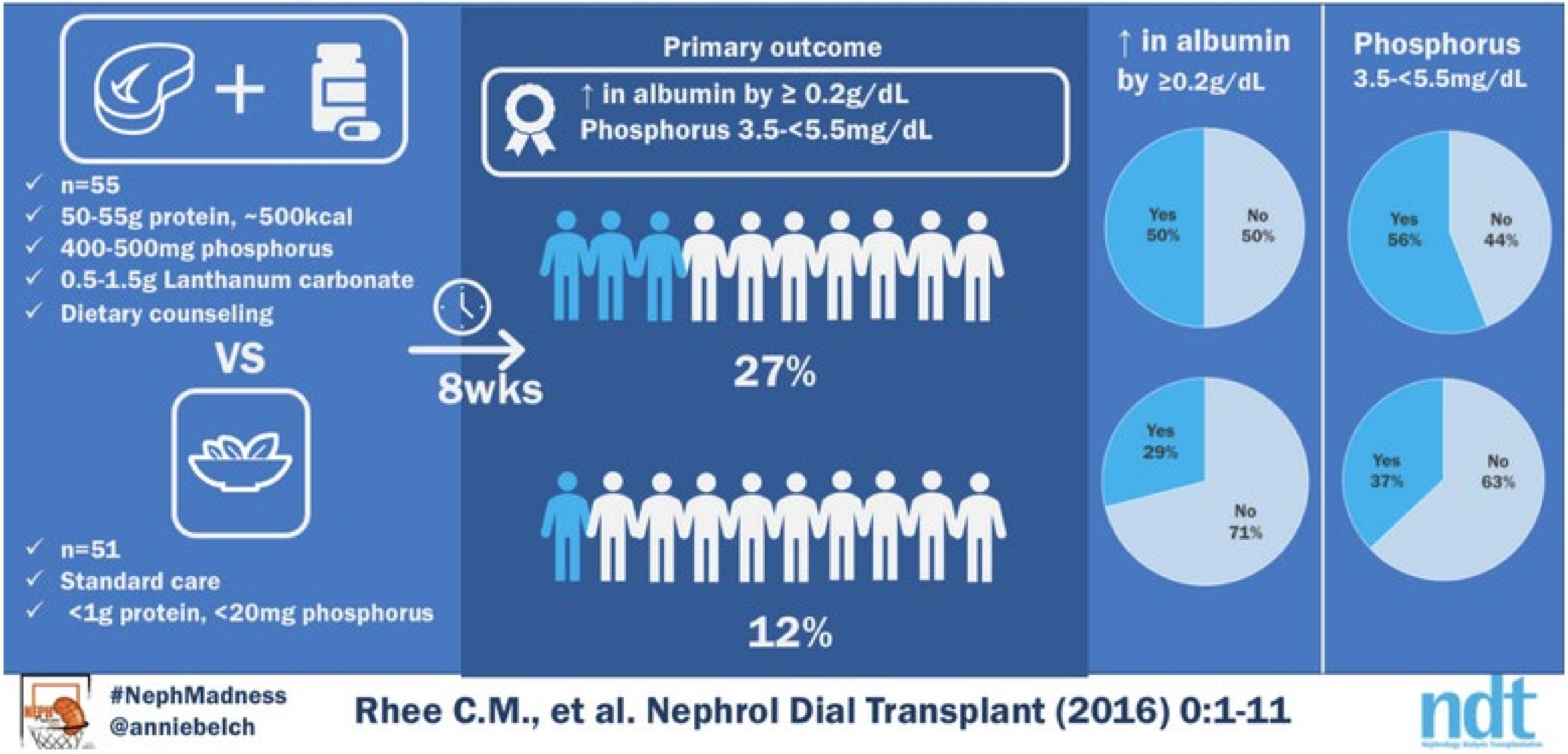
Dietary Restrictions in Dialysis Patients: Is There Anything Left to Eat?

Kamyar Kalantar-Zadeh,*†‡†† Amanda R. Tortorici,*† Joline L. T. Chen,*† Mohammad Kamgar,§ Wei-Ling Lau,* Hamid Moradi,*† Connie M. Rhee,* Elani Streja,*† and Csaba P. Kovesdy¶**

*Division of Nephrology and Hypertension, Harold Simmons Center for Kidney Disease Research and Epidemiology, University of California Irvine, Orange, California, †Long Beach Veterans Affairs Healthcare System, Long Beach, California, ‡Department of Epidemiology, UCLA Fielding School of Public Health, University of California Los Angeles, Los Angeles, California, §Long Beach Memorial Medical Center, Long Beach, California, ¶Renal Division, University of Tennessee Health Science Center, Memphis, Tennessee, **Memphis Veterans Affairs Medical Center, Memphis, Tennessee, and ††Los Angeles Biomedical Research Institute at Harbor-UCLA, Torrance, California

Kalantar, Ikizler, ***Journal of Renal Nutrition*** 2013.
Kalantar…Rhee…Kovesdy, ***Seminars in Dialysis*** 2015.

Impact of high-protein meals during treatment in hemodialysis patients with hypoalbuminemia: FrEDI trial



Effect of high-protein meals during hemodialysis combined with lanthanum carbonate in hypoalbuminemic dialysis patients: findings from the FrEDI randomized controlled trial

Nephrol Dial Transplant (2016) 0: 1–11
doi: 10.1093/ndt/gfw323

ndt
Nephrology Dialysis Transplantation

Effect of high-protein meals during hemodialysis combined with lanthanum carbonate in hypoalbuminemic dialysis patients: findings from the FrEDI randomized controlled trial

Connie M. Rhee[1], Amy S. You[1], Tara Koontz Parsons[2], Amanda R. Tortorici[1], Rachelle Bross[2], David E. St-Jules[3], Jennie Jing[1], Martin L. Lee[4], Debbie Benner[5], Csaba P. Kovesdy[6,7], Rajnish Mehrotra[8], Joel D. Kopple[4,9,10] and Kamyar Kalantar-Zadeh[1,2,4]

Rhee et al. ***NDT*** 2016.

Study Flow Diagram

234 hemodialysis patients screened across 8 Southern California outpatient dialysis units.

178 hemodialysis patients signed consent forms.

110 hemodialysis patients met eligibility criteria:
- Hypoalbuminemic (serum albumin <4.0 g/dL) at study entry (1st laboratory test).

Randomization

High-Protein Hemodialysis Meal
N=55

ratio

High-Protein Meal

anthanum
Phosphorus Binders

8-Week Study Period

Follow-Up Visit

Low-Protein Hemodialysis Meal
N=55

4 patients excluded due to:

Dietary cou
↑ Protein

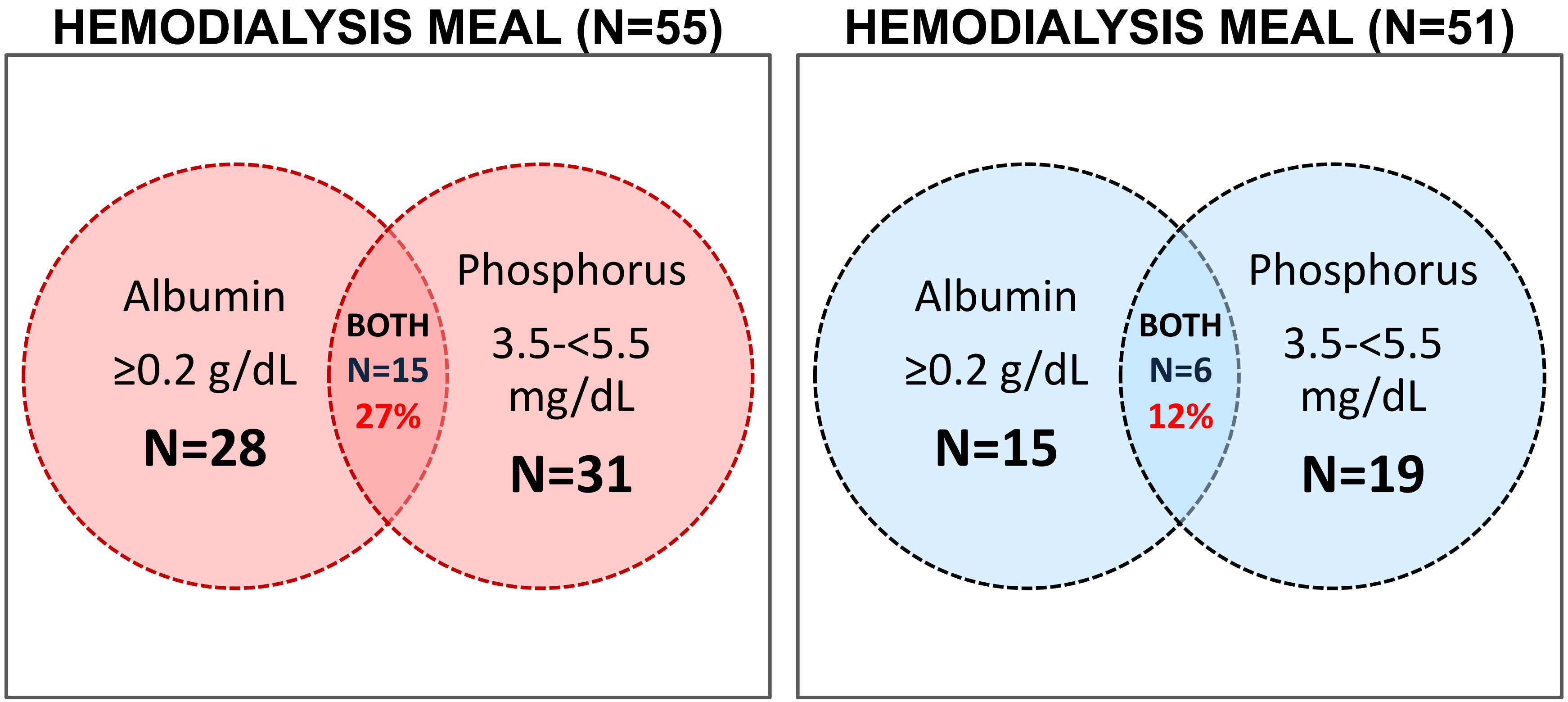
Low-Protein Meal

Non-Lanthanum
Phosphorus Binders

Rhee et al. ***NDT*** 2016.
Courtesy of Ms. Amy You.

Rhee … Kalantar-Zadeh, ***Nephol Dial Transplant*** 2016 [epub]

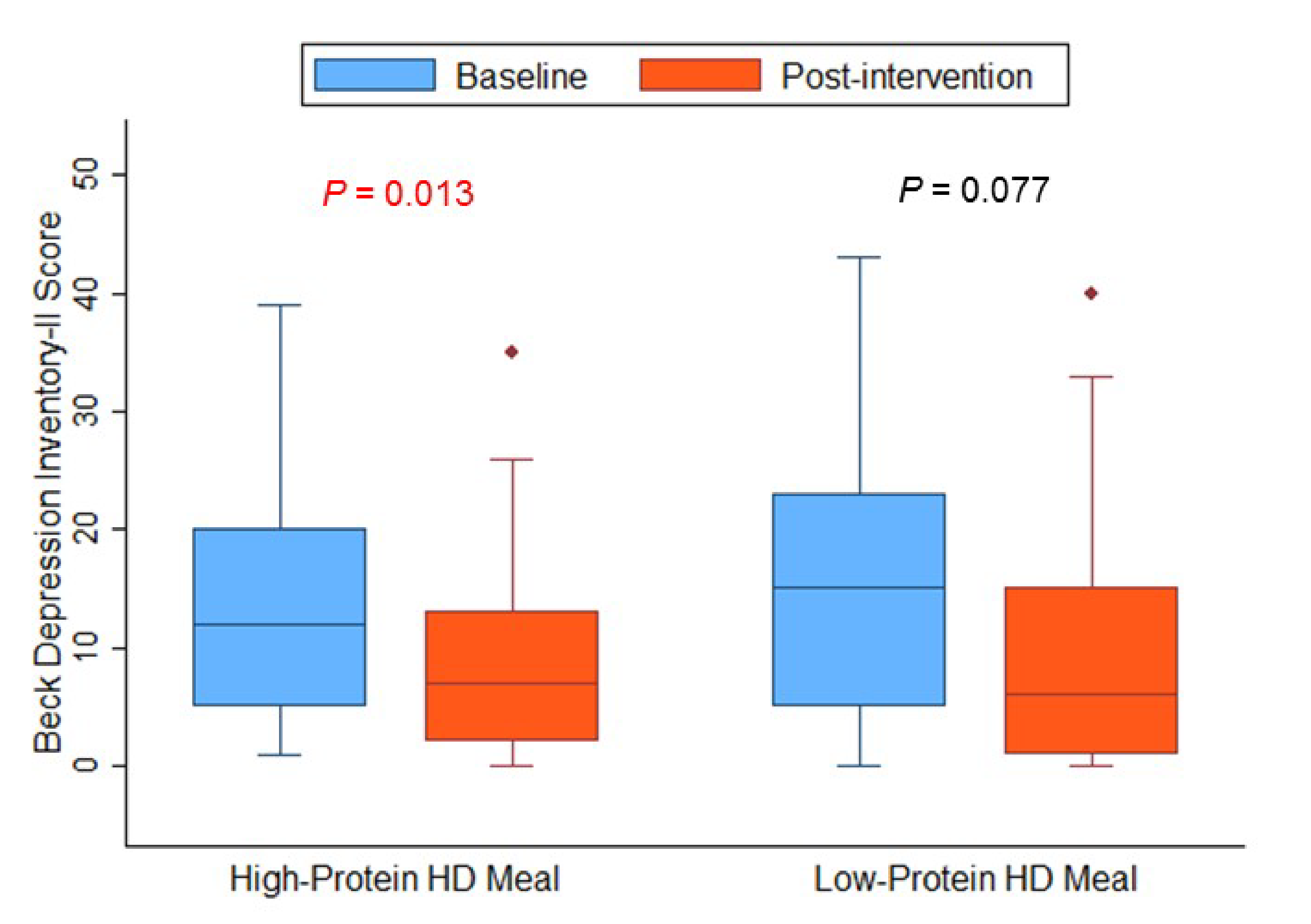
Increase in Serum Albumin ≥0.2 g/dL, while Serum Phosphorus remains in 3.5-<5.5 mg/dL range



27% of high-protein and 12% of low-protein hemodialysis meal groups achieved the primary outcome (chi-square p-value = 0.045).

Rhee et al. ***NDT*** 2016.
Courtesy of Ms. Amy You.

Improvement in patient-centered outcomes & HRQOL



Okazaki, Rhee, Narasaki, Shen, Shah, Dukkipati, Dai, Tong, Adler, Kopple, Kalantar. ***2023 ASN Kidney Week abstract***.

Oral nutritional supplementation during dialysis

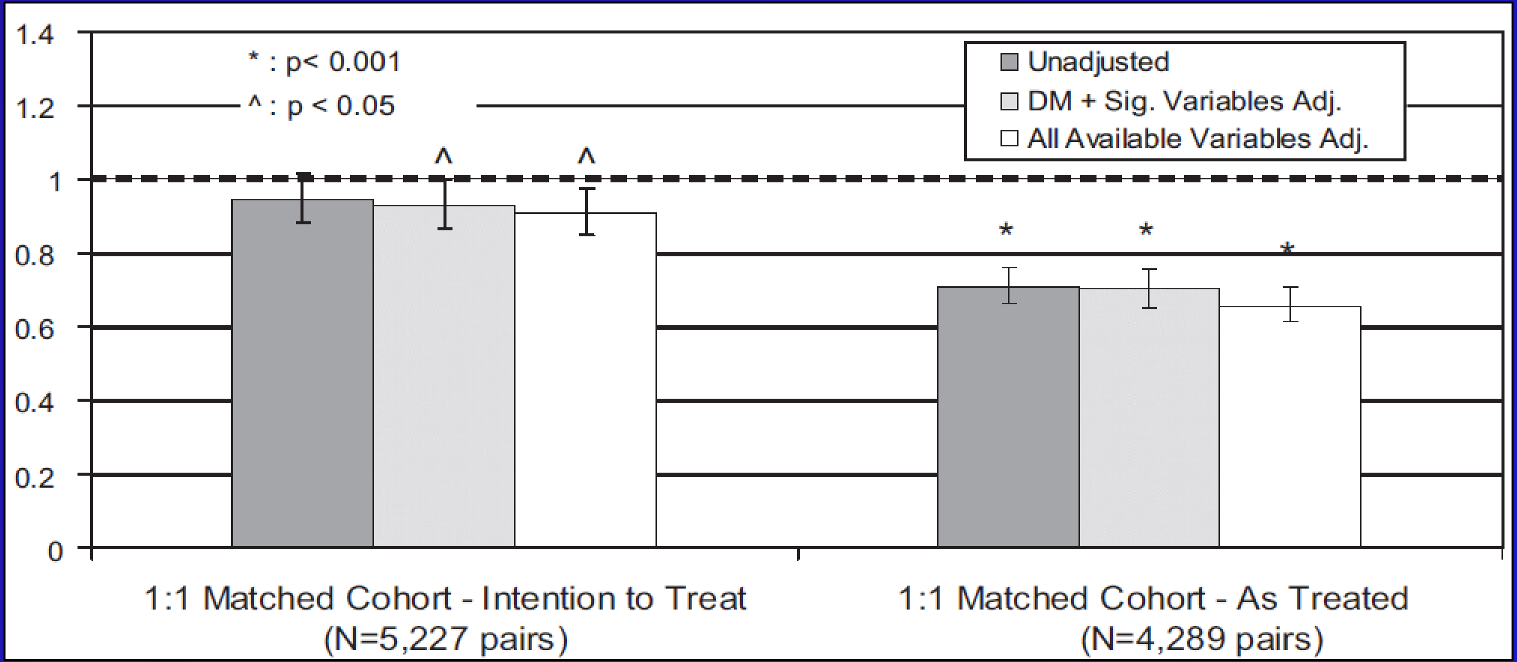
AJKD

Original Investigation

Outcomes Associated With Intradialytic Oral Nutritional Supplements in Patients Undergoing Maintenance Hemodialysis: A Quality Improvement Report

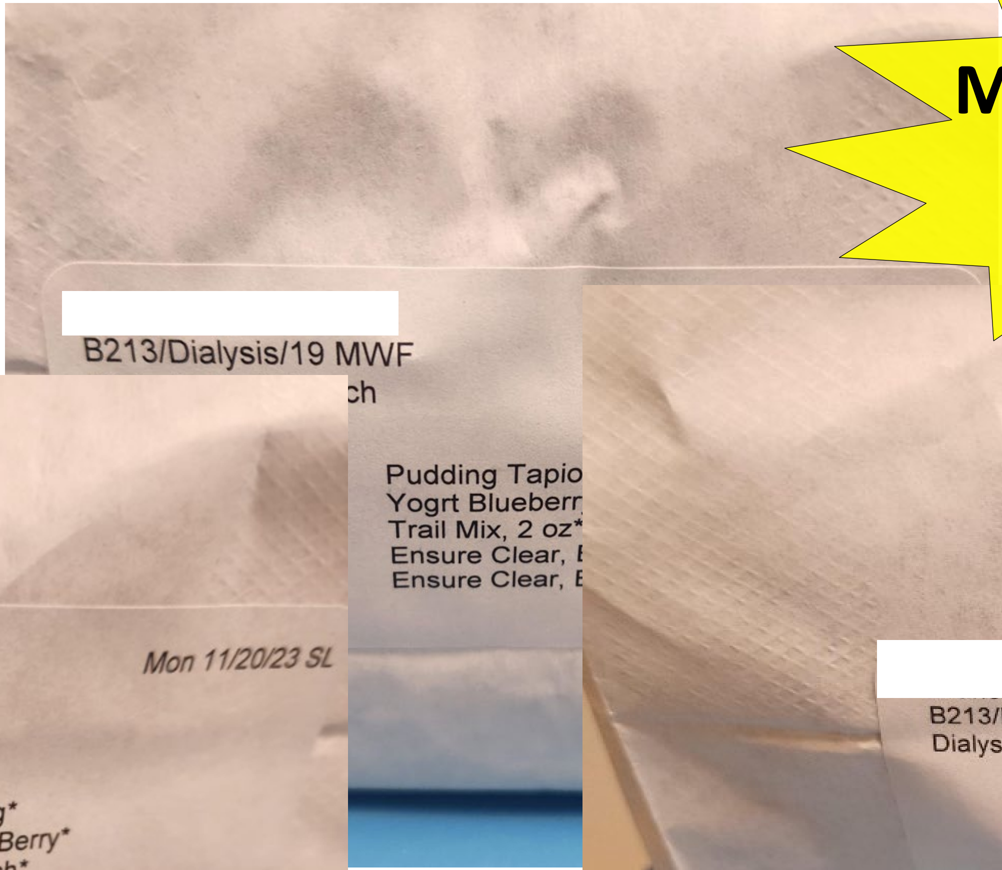
Eduardo Lacson Jr, MD, MPH, Weiling Wang, MS, Barbara Zebrowski, MS, RD, CSR, LDN, Rebecca Wingard, RN, MSN, CNN, and Raymond M. Hakim, MD, PhD

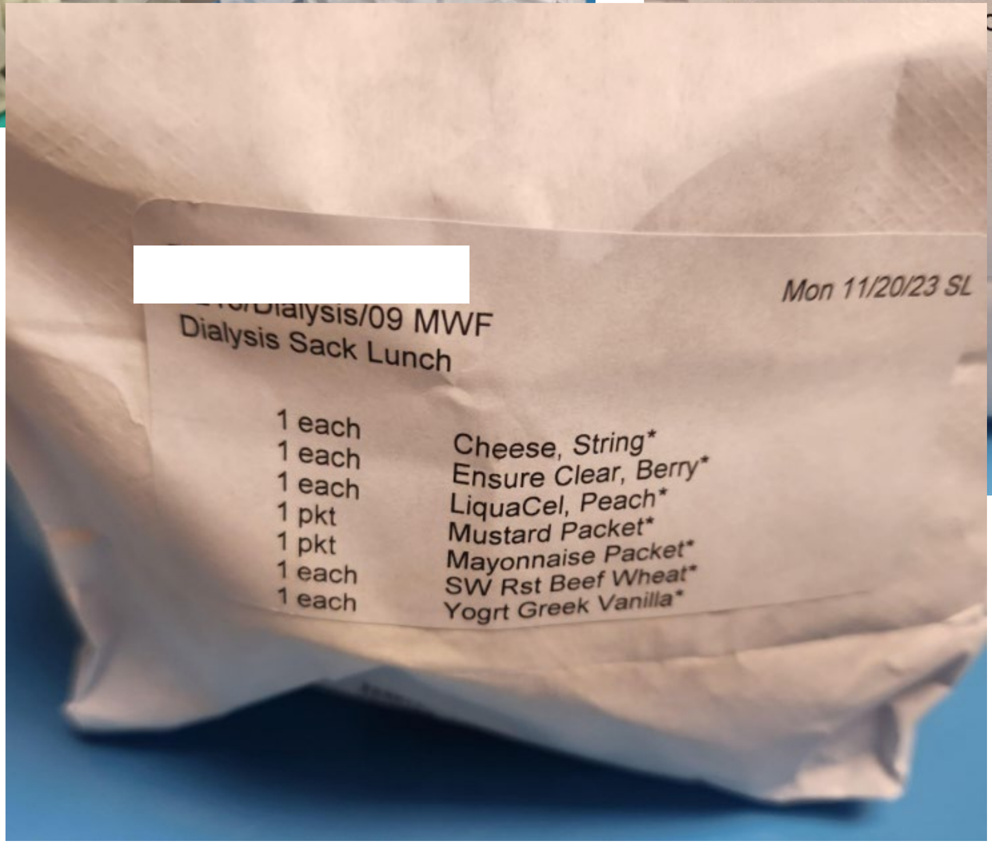
Monitored intradialytic ONS associated with ↑ survival in patients with serum albumin ≤3.5g/dl.

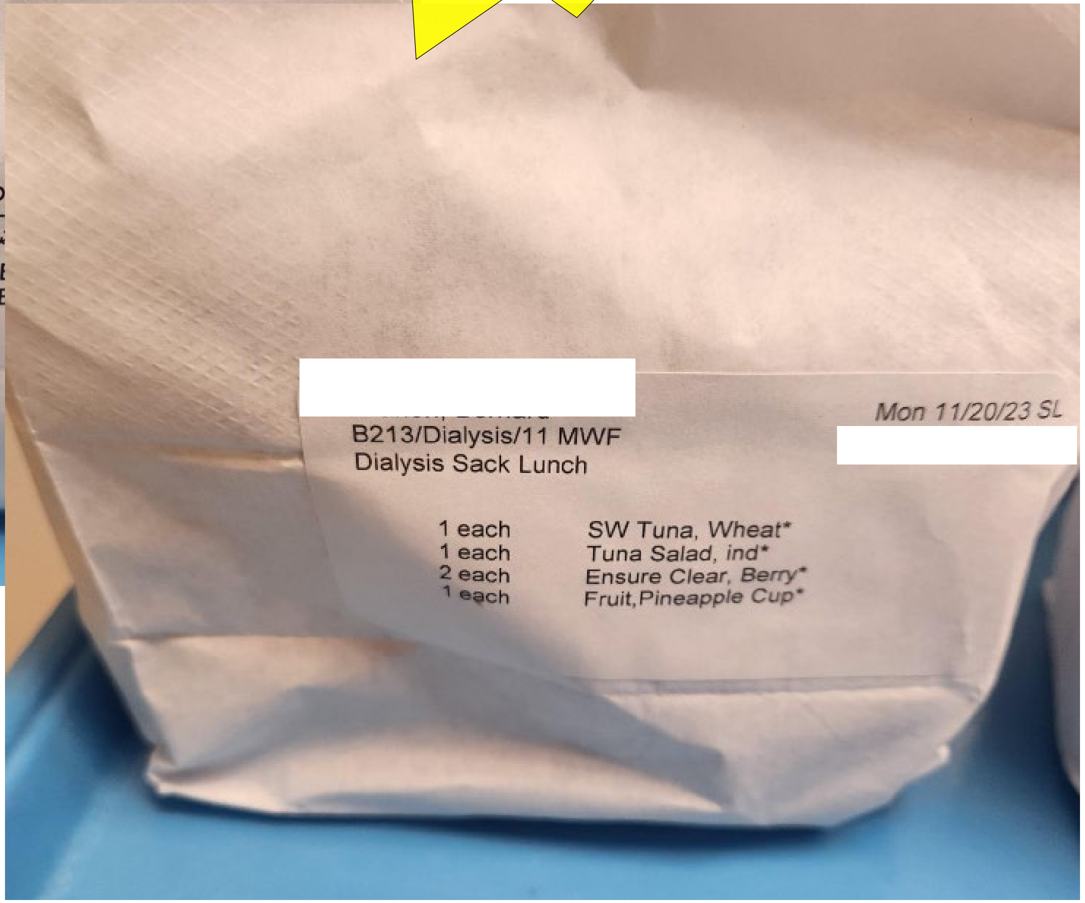


Lacson et al. ***AJKD*** *2012.*

My dialysis clinic







Eating during HD: ISRNM recommendations

Eating During Hemodialysis Treatment: A Consensus Statement From the International Society of Renal Nutrition and Metabolism

Brandon M. Kistler, PhD, RD,[*] Debbie Benner, MA, RD, CSR,[†] Jerrilynn D. Burrowes, PhD, RD, CDN,[‡] Katrina L. Campbell, RD, PhD,[§] Denis Fouque, MD, PhD,[¶] Giacomo Garibotto, MD,[**] Joel D. Kopple, MD,[††,‡‡,§§] Csaba P. Kovesdy, MD,[¶¶] Connie M. Rhee, MD, MSc,[***] Alison Steiber, RD, PhD,[†††] Peter Stenvinkel, MD, PhD,[‡‡‡] Pieter ter Wee, MD,[§§§] Daniel Teta, MD,[¶¶¶] Angela Y. M. Wang, MD,[****] and Kamyar Kalantar-Zadeh, MD, MPH, PhD[***]

Kistler…Rhee et al. *JReN* 2018.

Practical Guidelines for Eating During Treatment
Provision of meals during hemodialysis treatment should be the default practice and standard-of-care in all dialysis centers. • Hemodialysis patients should consider eating during treatment if they ○ are hemodynamically stable ○ have no contraindiction for eating during hemodialysis (see in the following) Patient characteristics • Patients should consider eating outside of treatment if they ○ have low blood pressure during treatment ○ frequently coughing or risk of choking ○ undergoing current bout of diarrhea that can be aggravated by eating ○ prone to stomach pain, indigestion, nausea, or vomiting during treatment ○ diagnosed autonomic dysfunction that may be precipitated by eating Position • Patients should be encouraged to eat in an upright position Food characteristics • Risk of hypotension may be greater with ○ larger meals ○ high amounts of simple carbohydrates ○ hot as opposed to cold food ○ lack of caffeinated items such as coffee • Patients should be encouraged to choose foods ○ high in protein and low in phosphorus (phosphorus to protein ration <15 mg/g) ○ fit within the renal diet ○ do not increase choking risk ○ do not increase thirst ○ do not need to be stored, chilled, or prepared in-center ○ can be eaten with 1 hand ○ will not make a mess ○ do not have a strong odor • Patients should be prepared to take phosphorus binder with food • Patients should strive to avoid large variations in intake from treatment to treatment

Kistler…Rhee et al. ***JReN*** 2018.

Individualized approach to eating during HD

Checklist

- Hemodynamically unstable
- Have low blood pressure during treatment
- Frequently coughing or at risk of choking
- Undergoing current bout of diarrhea that can be aggravated by eating
- Prone to stomach pain, indigestion, nausea, or vomiting during treatment
- Diagnosed autonomic dysfunction that may be precipitated by eating

NO → Intradialytic eating

YES → Eating outside of HD treatment

Courtesy of Dr. Yoko Narasaki.

Kistler…Rhee et al. ***JReN*** 2018.

Multi-faceted management approaches

NUTRITIONAL SUPPORT

- Oral nutrional supplement
- IDPN
- TPN

Avoid excess restriction

Meals w/ dialysis

EXERCISE

- Interventions that increase physical activity

Aerobic, resistance, yoga

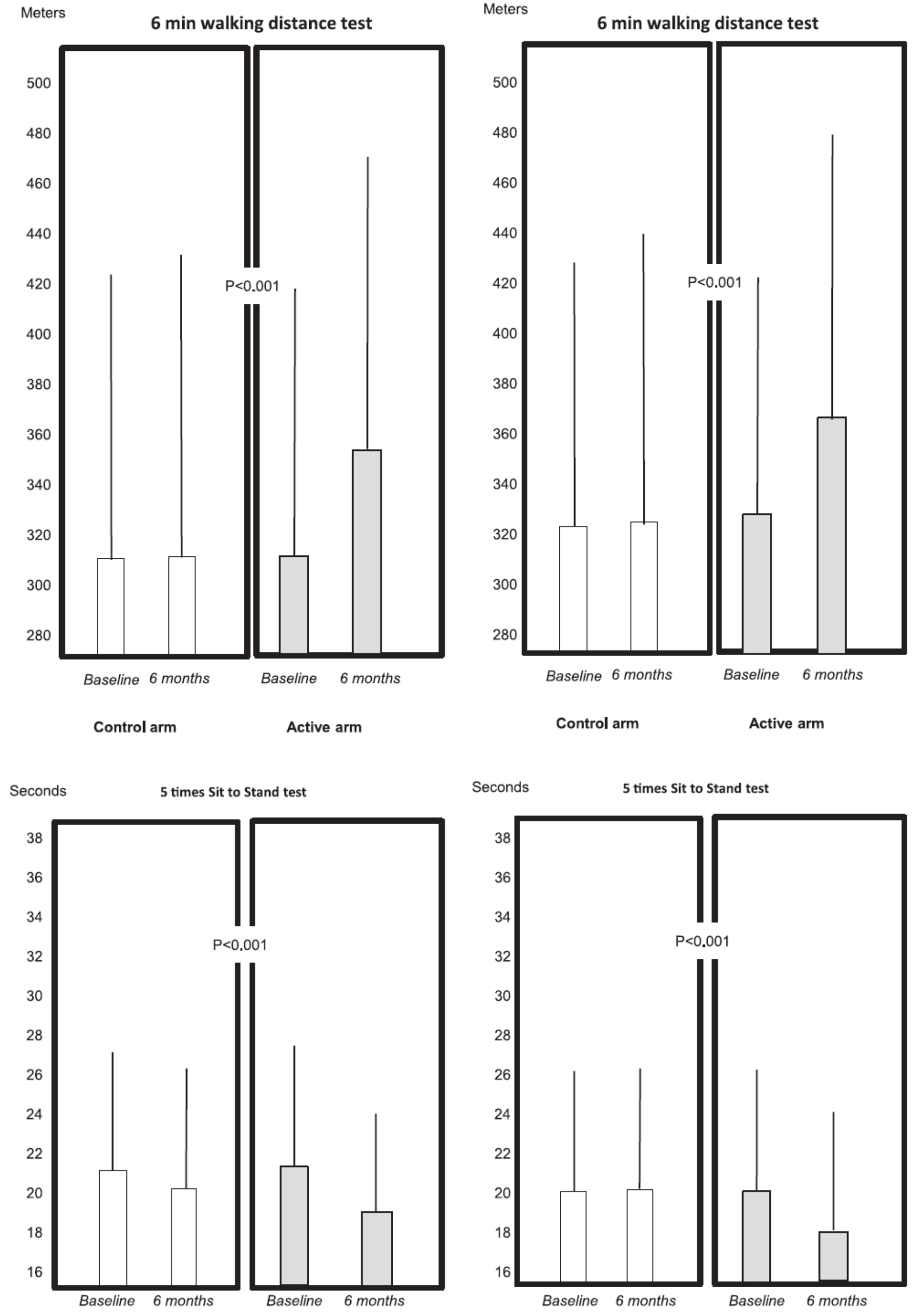
PHARMACO-THERAPIES

- Vitamin D
- Oral alkali
- Testosterone

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

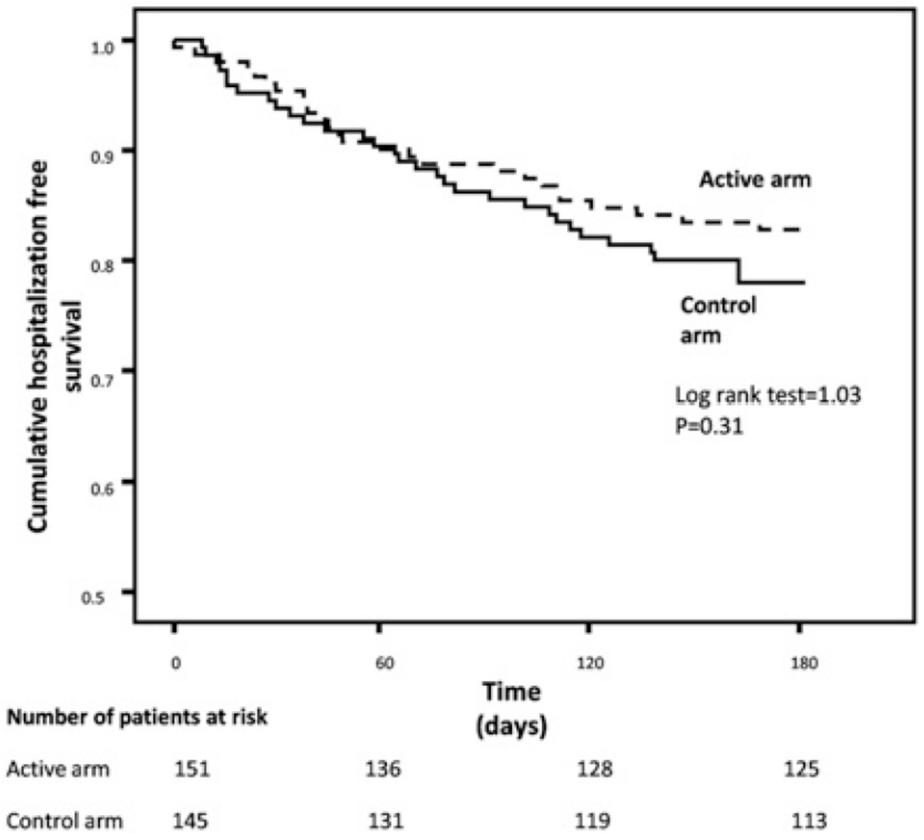
Exercise in Patients on Dialysis: A Multicenter, Randomized Clinical Trial

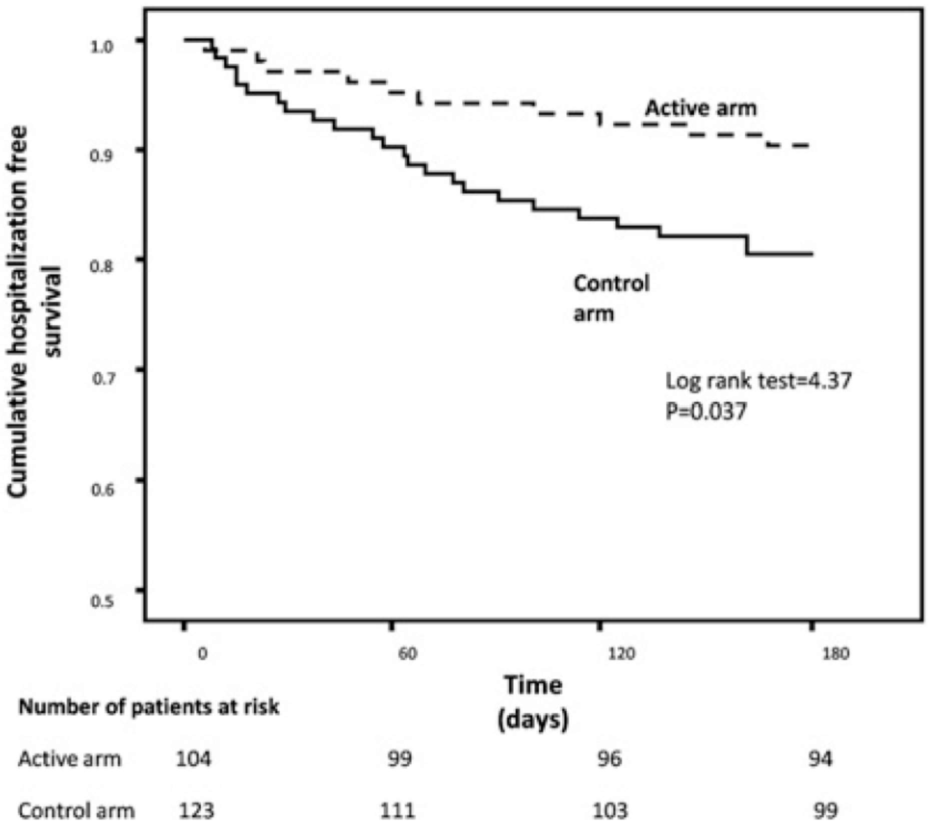
Fabio Manfredini,[*†] Francesca Mallamaci,[‡§] Graziella D'Arrigo,[‡] Rossella Baggetta,[‡] Davide Bolignano,[‡] Claudia Torino,[‡] Nicola Lamberti,[*] Silvio Bertoli,[‖] Daniele Ciurlino,[‖] Lisa Rocca-Rey,[‖] Antonio Barillà,[¶] Yuri Battaglia,[¶] Renato Mario Rapanà,[**] Alessandro Zuccalà,[**] Graziella Bonanno,[††] Pasquale Fatuzzo,[‡‡] Francesco Rapisarda,[‡‡] Stefania Rastelli,[‡‡] Fabrizio Fabrizi,[§§] Piergiorgio Messa,[§§] Luciano De Paola,[‖‖] Luigi Lombardi,[‖‖] Adamasco Cupisti,[¶¶] Giorgio Fuiano,[***] Gaetano Lucisano,[***] Chiara Summaria,[***] Michele Felisatti,[†] Enrico Pozzato,[†] Anna Maria Malagoni,[†] Pietro Castellino,[‡‡] Filippo Aucella,[†††] Samar Abd ElHafeez,[‡‡‡] Pasquale Fabio Provenzano,[‡] Giovanni Tripepi,[‡] Luigi Catizone,[¶] and Carmine Zoccali[‡]



Manfredini et al. *JASN* 2017.

Benefits of simple, personalized, home-based, low-intensity exercise program





- *Exercise intervention improved physical performance, quality of life, & survival in dialysis patients.*

Manfredini et al. ***JASN*** 2017.

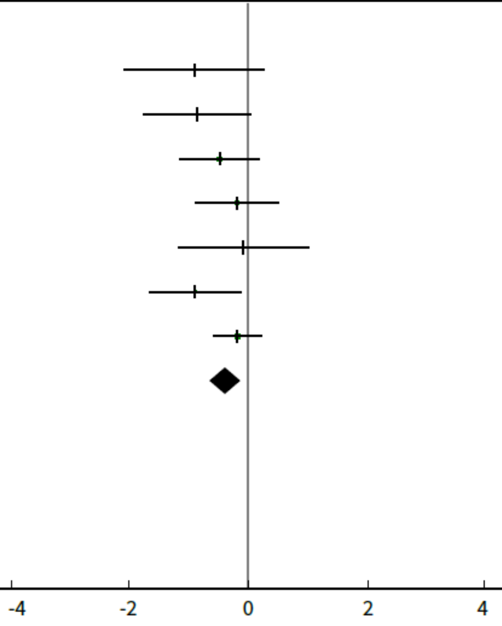
Cochrane Library

Cochrane Database of Systematic Reviews

Exercise training for adults with chronic kidney disease (Review)

Heiwe S, Jacobson SH

Study or subgroup	Control N	Control Mean(SD)	Exercise N	Exercise Mean(SD)	Weight	Std. Mean Difference Fixed, 95% CI
1.1.1 at 3 months						
Akiba 1995	6	17.6 (2.6)	7	20 (2.4)	1.47%	-0.9[-2.06,0.27]
Carmack 1995	11	10.9 (3.1)	10	14.4 (4.7)	2.45%	-0.85[-1.76,0.05]
Jong 2004	17	22.8 (5.5)	19	25.2 (4.3)	4.53%	-0.48[-1.14,0.19]
Koufaki 2002a	15	18.8 (4.9)	18	19.9 (6.3)	4.24%	-0.19[-0.87,0.5]
Parsons 2004	7	55 (26)	6	58 (44)	1.68%	-0.08[-1.17,1.01]
DePaul 2002	14	30 (10)	15	44 (19)	3.39%	-0.89[-1.66,-0.12]
van Vilsteren 2005	43	26.3 (10.8)	53	28 (8.8)	12.32%	-0.18[-0.58,0.22]
Subtotal ***	**113**		**128**		**30.08%**	**-0.39[-0.65,-0.13]**
Heterogeneity: Tau²=0; Chi²=5.09, df=6(P=0.53); I²=0%						
Test for overall effect: Z=2.96(P=0)						
1.1.2 at 4-6 months						



- *Exercise training improved physical fitness, cardiovascular parameters, serum albumin, and HRQOL.*

Multi-faceted management approaches

NUTRITIONAL SUPPORT
- Oral nutrional supplement
- IDPN
- TPN

Avoid excess restriction

Meals w/ dialysis

EXERCISE
- Interventions that increase physical activity

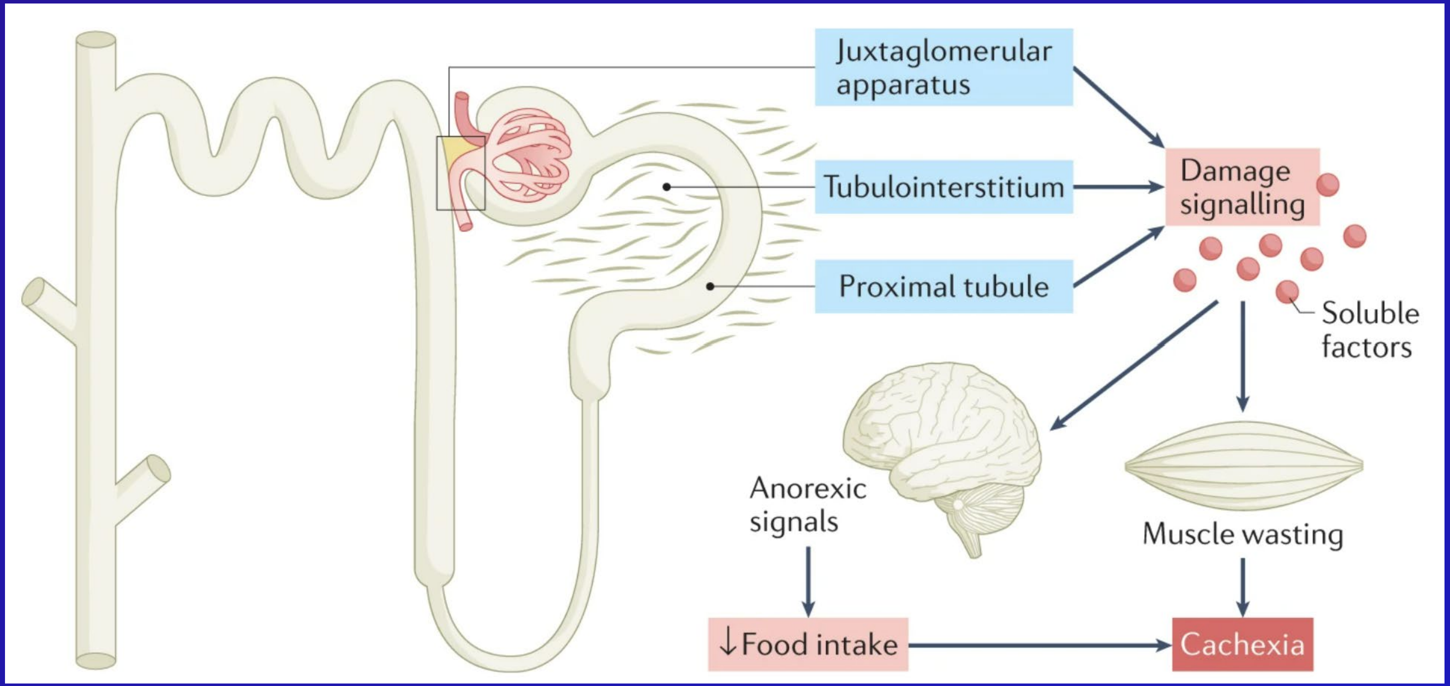
Aerobic, resistance, yoga

PHARMACO-THERAPIES
- Vitamin D
- Oral alkali
- Testosterone

Anti-catabolic therapy

Growth differentiation factor 15 (GDF15)

- Protein in the TGF-β family
  - Acts directly on hypothalamus
  - ↓'s food intake & energy expenditure
- In cancer-associated cachexia, ↑ GDF15 associated with
  - Satiety
  - Weight loss
  - Death



- ↑ Circulating GDF15 levels in kidney dysfunction.

Emerging data suggest that injured proximal tubule cells produce GDF15 as a link between the kidney and cachexia.

Wang et al, ***Nat Rev Endo*** 2021.
Mulderrig et al, ***Nature*** 2021.

Puelles, Huber, ***Nat Rev Neph*** 2022.

Characteristics associated with ↑ GDF15 in ESKD

Variable	Unadjusted		Case mix adjusted	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Case mix characteristics				
Age (Δ10 years)	**1.57 (1.25–1.98)**	**<0.001**	**1.58 (1.23–2.02)**	**<0.001**
Female	0.70 (0.39–1.28)	0.25	0.62 (0.33–1.19)	0.15
Black race	**0.39 (0.20–0.77)**	**0.007**	0.43 (0.17–1.07)	0.07
Hispanic	1.73 (0.96–3.12)	0.07	1.12 (0.48–2.58)	0.80
Diabetes	1.59 (0.88–2.88)	0.13	1.00 (0.49–2.02)	0.99
Dialysis vintage (Δ1 year)	0.97 (0.90–1.04)	0.40	0.99 (0.92–1.07)	0.79
Laboratory tests				
Serum albumin, Δ0.5 g/dL	0.76 (0.49–1.17)	0.21	0.77 (0.47–1.26)	0.30
Creatinine (mg/dL)	**0.89 (0.80–0.98)**	**0.02**	0.96 (0.85–1.10)	0.56
Phosphorus (mg/dL)	0.92 (0.75–1.11)	0.37	1.03 (0.84–1.27)	0.75
Hemoglobin (g/dL)	1.18 (0.89–1.57)	0.25	1.21 (0.88–1.68)	0.24
Body mass index	**0.75 (0.58, 0.96)**	**0.02**	**0.75 (0.56, 0.99)**	**0.02**
Normalized protein catabolic rate (g/kg/day)	1.05 (0.86, 1.28)	0.61	0.99 (0.78, 1.24)	0.90

You, Kalantar…Rhee, ***Cardiorenal Medicine*** 2017.

CardioRenal Medicine

Cardiorenal Med 2017;7:158–168
DOI: 10.1159/000455907
Received: November 20, 2016
Accepted: January 3, 2017
Published online: February 2, 2017
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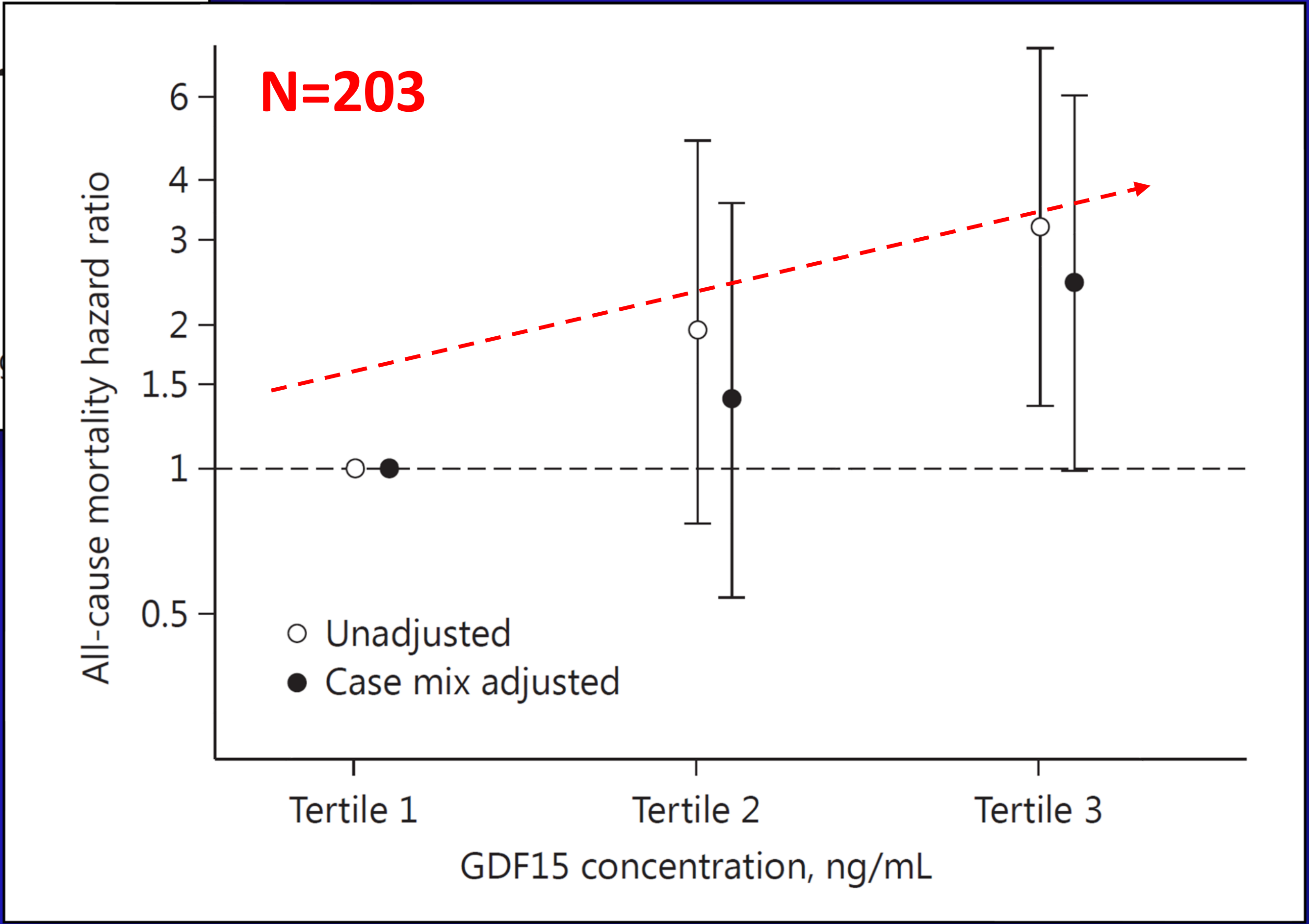
www.karger.com/crm

Original Paper

Association of Growth Differentiation Factor 15 with Mortality in a Prospective Hemodialysis Cohort

Amy S. You[a] Kamyar Kalantar-Zadeh[a] Lorena Lerner[b] Tracy Nakata
Nancy Lopez[a] Lidia Lou[a] Mary Veliz[a] Melissa Soohoo[a] Jennie Jin
Frank Zaldivar[c] Jeno Gyuris[b] Danh V. Nguyen[c] Connie M. Rhee[a]

Ms. Amy You



You, Kalantar...Rhee, ***Cardiorenal Medicine*** 2017.

↑ GDF15 associated with worse Malnutrition Inflammation Score

MALNUTRITION INFLAMMATION SCORE (M.I.S.)

(A) Patients' related medical history:

1- Change in end dialysis dry weight (overall change in past 3-6 months):

0	1	2	3
No decrease in dry weight or weight loss <0.5 kg	Minor weight loss (≥0.5 kg but <1 kg)	Weight loss more than one kg but <5%	Weight loss >5%

2- Dietary intake:

0	1	2	3

Malnutrition Inflammation Score

- ✓ Validated and quantitative nutritional assessment tool used to estimate PEW.
- ✓ Subjective Global Assessment, BMI, serum albumin, and TIBC.
- ✓ Scored from 0 (normal) to 30 (severely malnourished).

6- Decreased fat stores or loss of subcutaneous fat (below eyes, triceps, biceps, chest):

0	1	2	3
Normal (no change)	mild	moderate	Severe

7- Signs of muscle wasting (temple, clavicle, scapula, ribs, quadriceps, knee, interosseous):

0	1	2	3
Normal (no change)	mild	moderate	Severe

(C) Body mass index:

8- Body mass index: BMI = Wt(kg) / Ht^2(m)

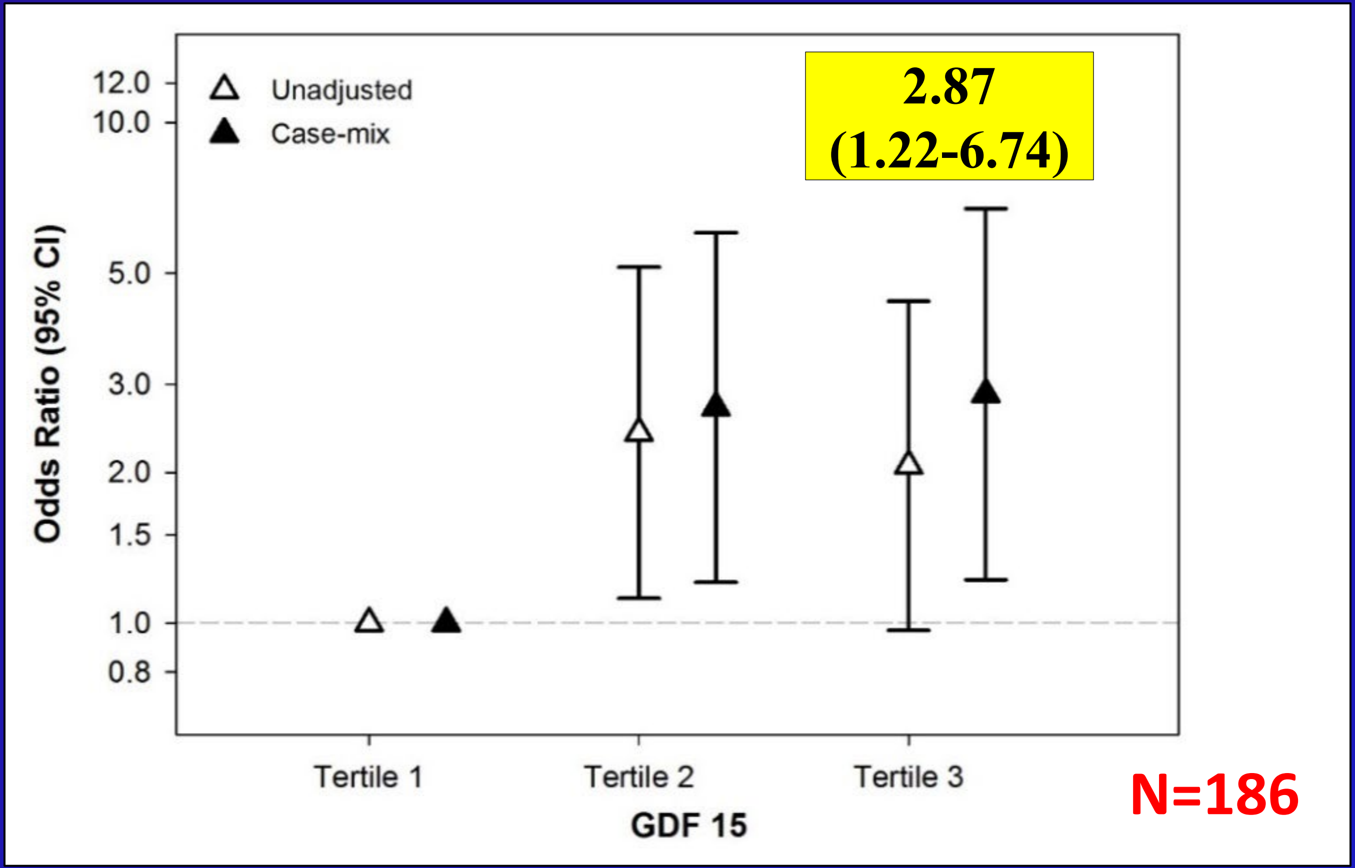
0	1	2	3
BMI≥20 kg/m^2	BMI: 18-19.99 kg/m^2	BMI: 16-17.99 kg/m^2	BMI<16 kg/m^2

(D) Laboratory Parameters:

9- Serum albumin:

0	1	2	3
Albumin≥ 4.0 g/dL	Albumin: 3.5-3.9 g/dL	Albumin: 3.0-3.4 g/dL	Albumin: <3.0 g/dL

10- Serum TIBC (total Iron Binding Capacity): ♣



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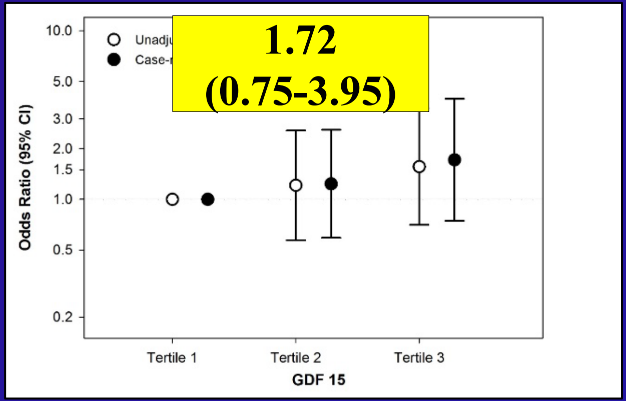
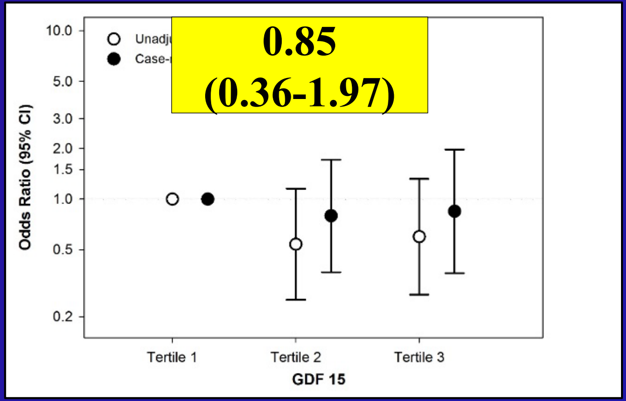
↑ GDF15 levels associated with higher (worse) Malnutrition Inflammation Score.

↑ GDF15 linked with worse body anthropometry

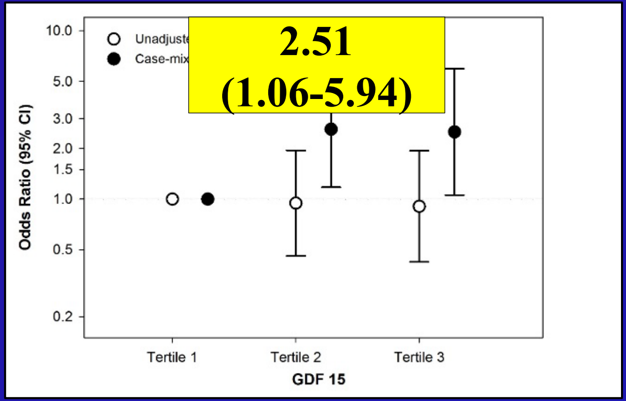
Low Biceps



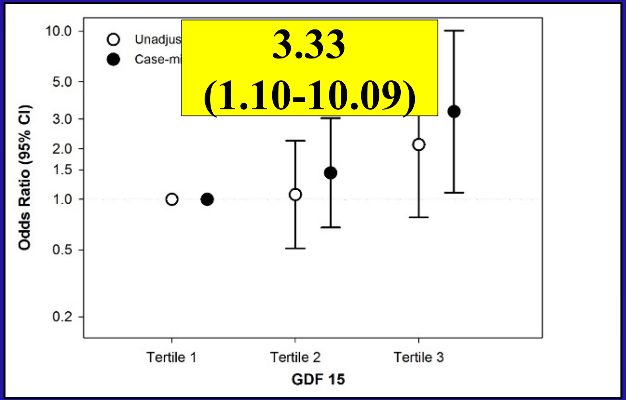
Low Triceps



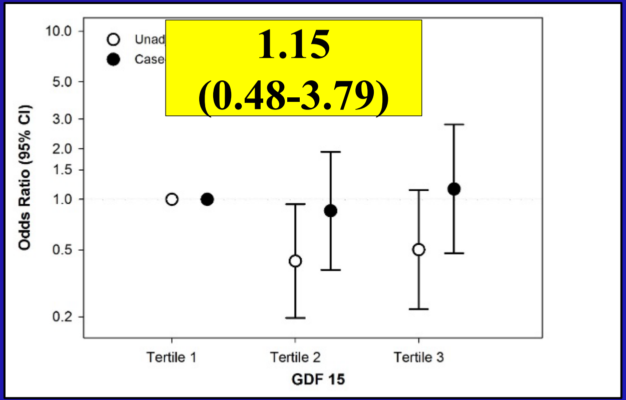
Low MAC



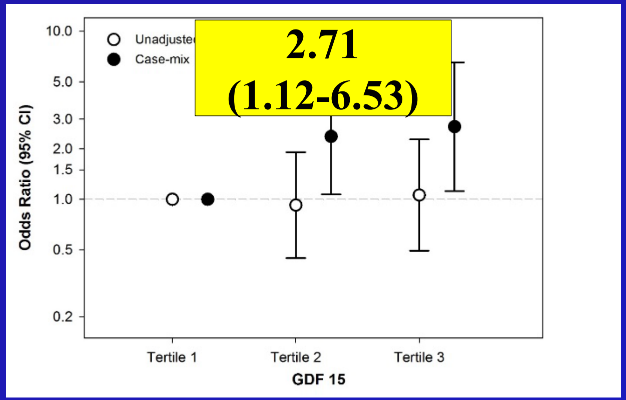
Low NIR Body Fat %



Low Waist Circumference



Low BMI



Higher GDF15 levels associated with lower mid-arm circumference, near infrared body fat %, and BMI.

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Ponsegromab for the Treatment of Cancer Cachexia

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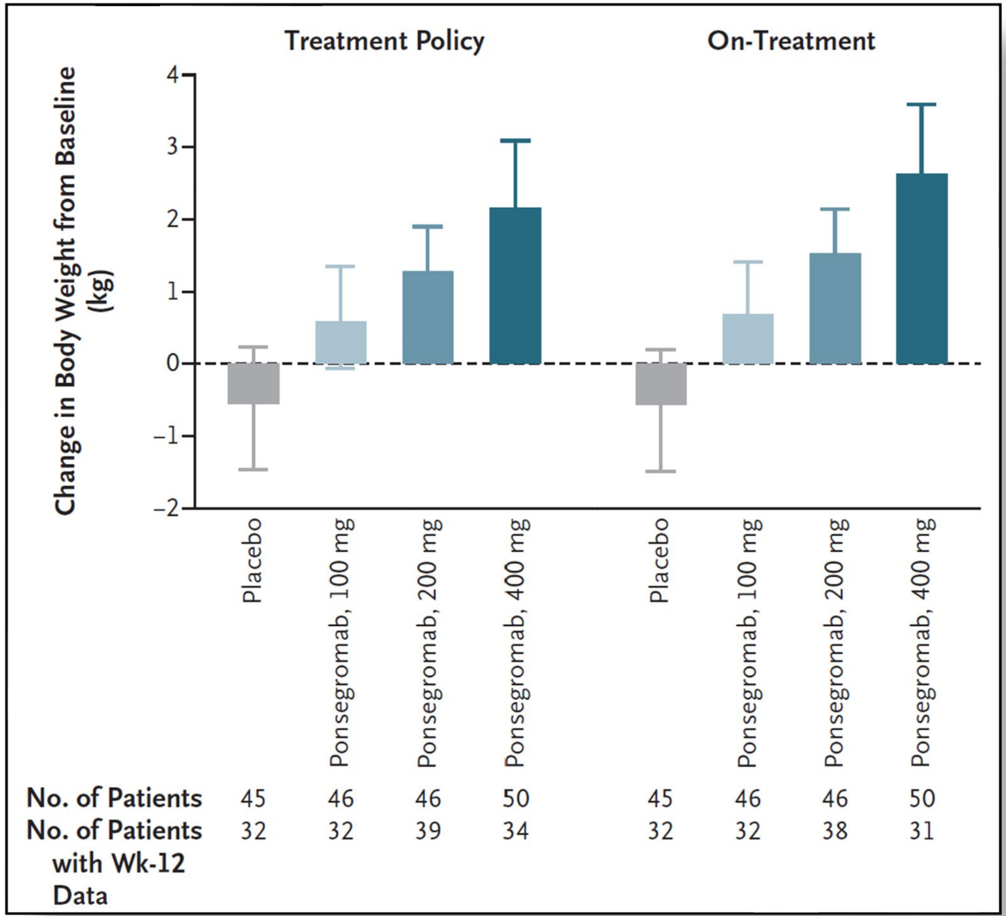
Anti-GDF-15 monoclonal antibody increased body weight, increased physical activity, and decreased cachexia symptoms.



Conclusions

- The pathogenesis of CKD-associated sarcopenia is complex and multifactorial.
  - In progressive CKD, loss of muscle strength is independent of muscle wasting.
- While there is overlap between frailty & sarcopenia, frailty constitutes a broader constitutional spectrum than sarcopenia.
  - Physical inactivity most modifiable frailty component in CKD.
- Protein-energy wasting is a highly prevalent condition associated with substantial morbidity & mortality in CKD patients.
  - Characterized by a maladaptie response to decreased protein & energy intake.
  - Dialysis patients are in negative nitrogen balance due to decreased dietary intake, increased catabolism, inflammation, insulin resistance, & loss of AA's in the dialysate.
- Screening tools for sarcopenia, frailty, & PEW can facilitate early identification & intervention.
- Further research is needed to evaluate the efficacy & safety of multi-disciplinary interventions that mitigate the complicatons of sarcopenia, frailty, & PEW.

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