Active Lives, Stronger Kidneys: How Exercise Shapes Cognitive and Cardiorenal Health in Chronic Kidney Disease

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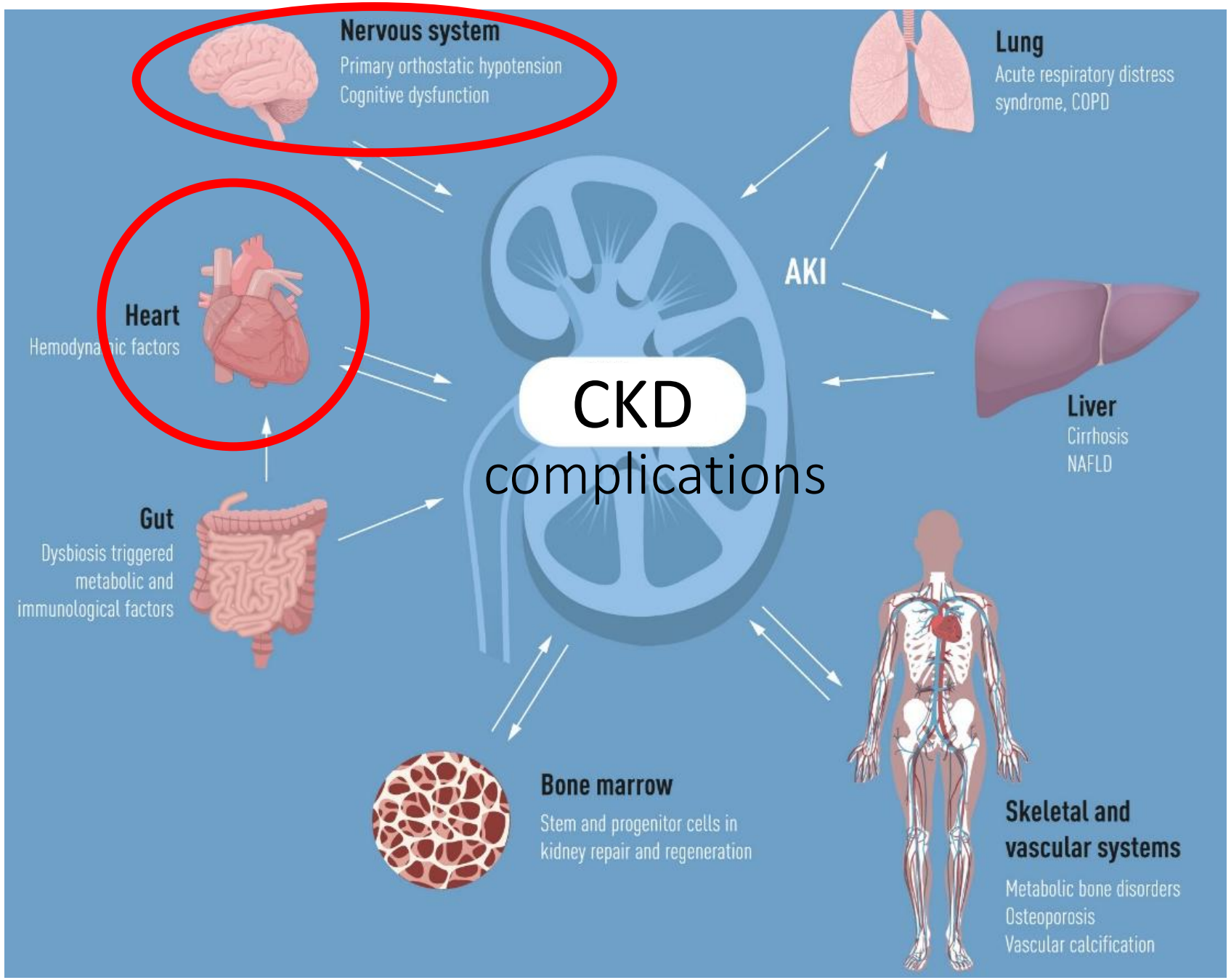
Disclaimer

- No conflict of interests

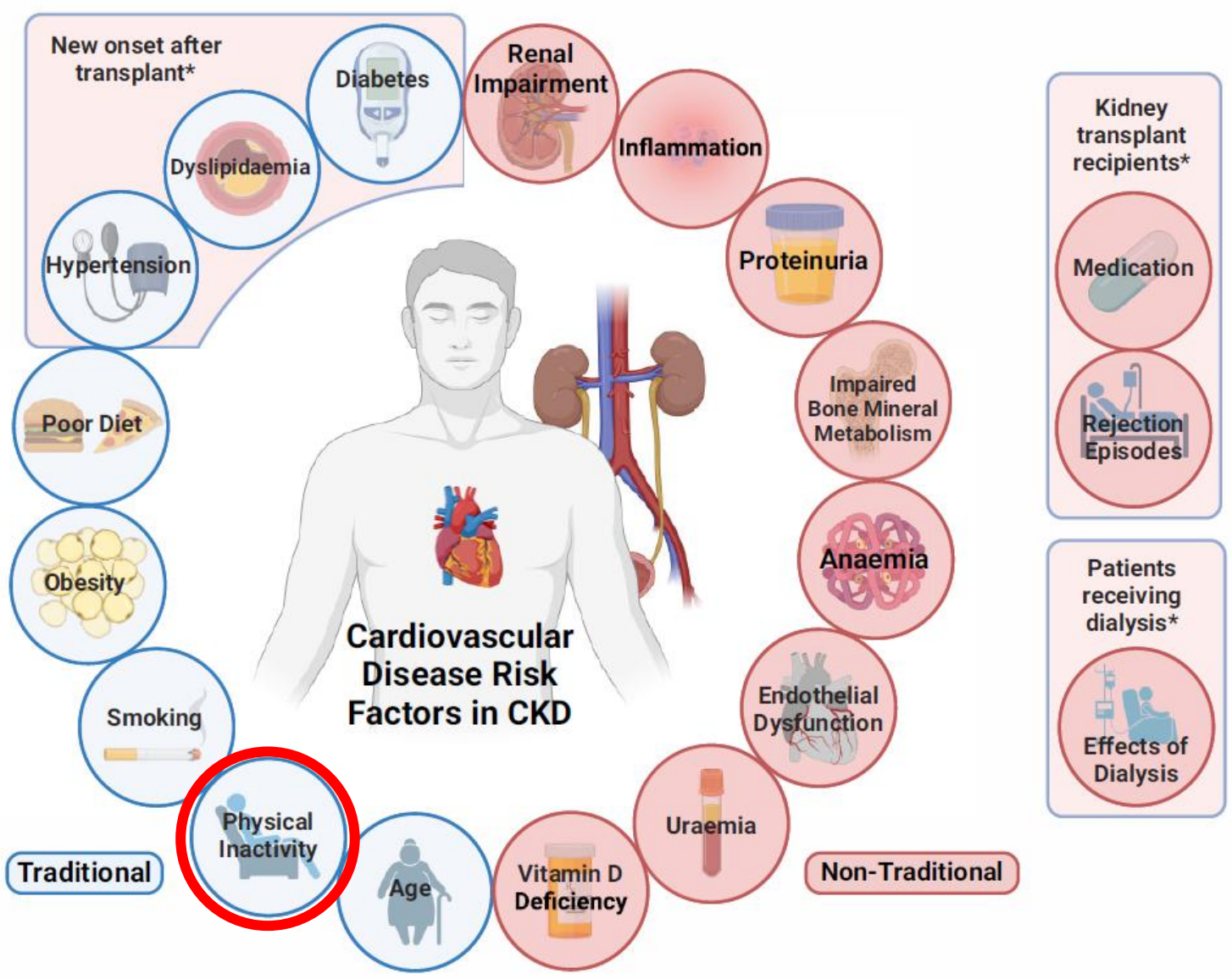
Outlines

- Physical activity (PA)
  - Benefit
- Muscle kidney crosstalk
- PA in CKD
  - Pathophysiology
  - Outcomes
- Interaction between PA and Cognitive Impairment in CKD



J Intern Med. 2025 Nov;298:368-391.

CV Risk Factors in CKD



Nephrol Dial Transplant. 2025 Oct 30;40(11):2011-2025

Panel 1: Health benefits of physical activity in adults[3–5]

Strong evidence of reduced rates of:

- All-cause mortality
- Coronary heart disease
- High blood pressure
- Stroke
- Metabolic syndrome
- Type 2 diabetes
- Breast cancer
- Colon cancer
- Depression
- Falling

Strong evidence of:

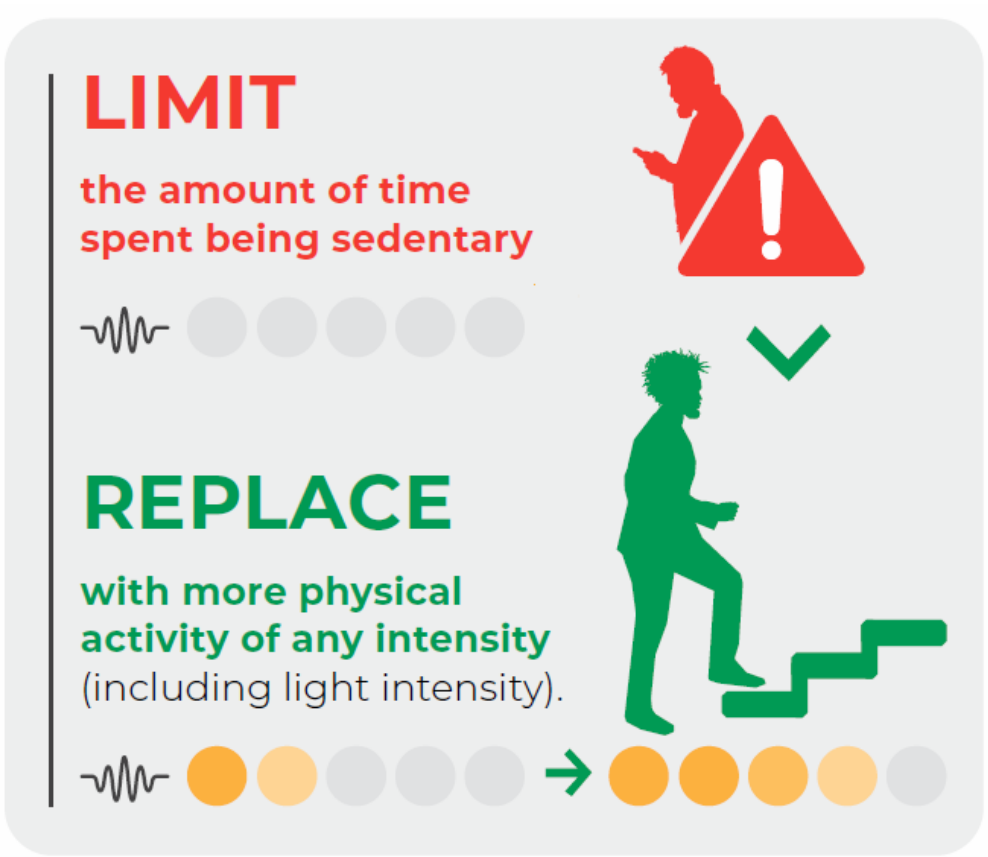
- Increased cardiorespiratory and muscular fitness
- Healthier body mass and composition
- Improved bone health
- Increased functional health
- Improved cognitive function

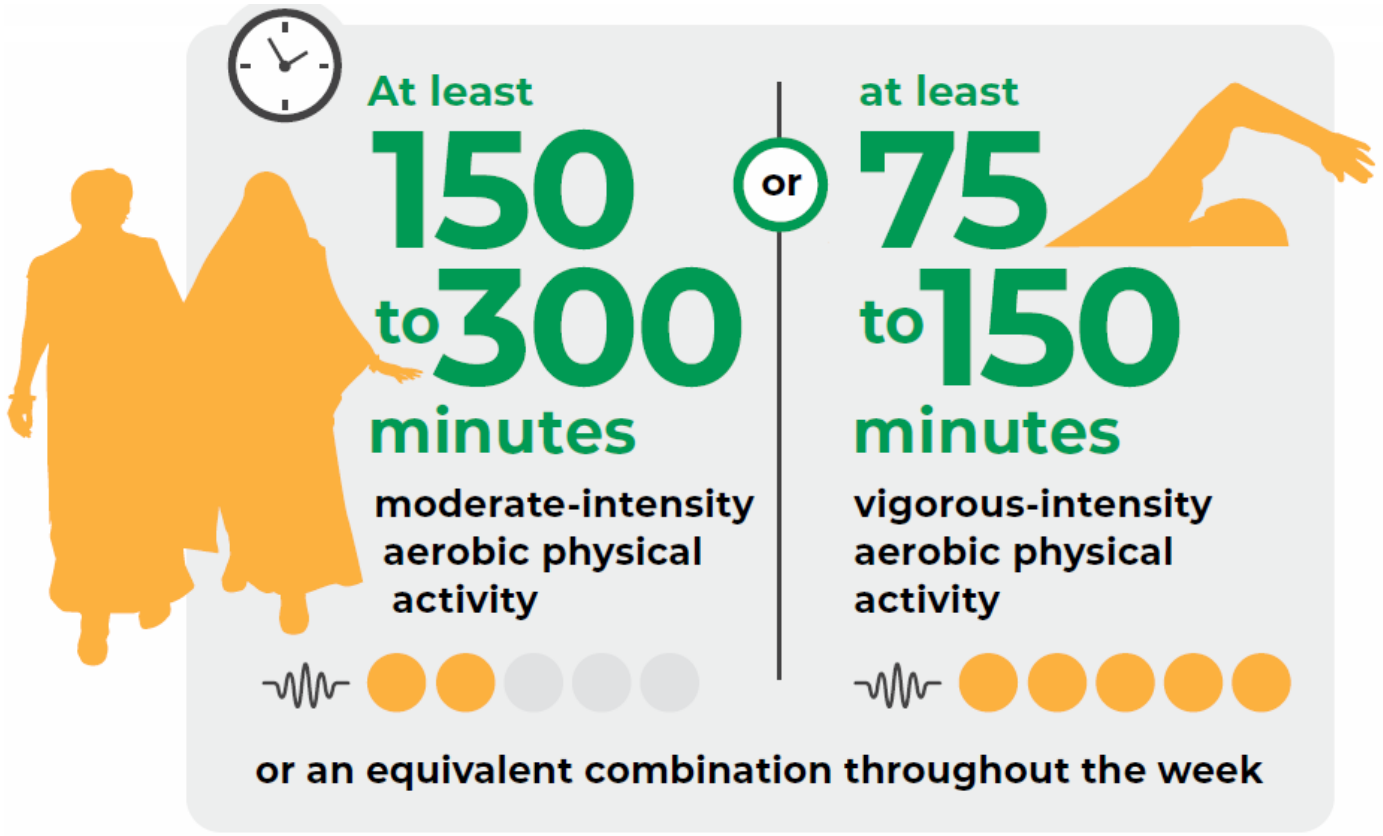
***Lancet* 2012; 380: 219–29**

✓ **6-10%** of all deaths from noncommunicable diseases attributable to **physical inactivity**

✓ **4th** leading cause of death worldwide

Every Move Counts





World Health Organization

1 MET=1 kcal/kg/hr; MET-hr=Volume

Physical activity	MET
Light intensity activities	**< 3**
sleeping	0.9
watching television	1.0
writing, desk work, typing	1.8
walking, 1.7 mph (2.7 km/h), level ground, strolling, very slow	2.3
walking, 2.5 mph (4 km/h)	2.9
Moderate intensity activities	**3 to 6**
bicycling, stationary, 50 watts, very light effort	3.0
walking 3.0 mph (4.8 km/h)	3.3
calisthenics, home exercise, light or moderate effort, general	3.5
walking 3.4 mph (5.5 km/h)	3.6
bicycling, <10 mph (16 km/h), leisure, to work or for pleasure	4.0
bicycling, stationary, 100 watts, light effort	5.5
Vigorous intensity activities	**> 6**
jogging, general	7.0
calisthenics (e.g. pushups, situps, pullups,jumping jacks), heavy, vigorous effort	8.0
running jogging, in place	8.0
rope jumping	10.0

1 hr

30 min

Ainsworth's 2011 Compendium of Physical Activities. Med Sci Sports Exerc. 2011;43:1575-81

NHANES-II: Low PA links to risks of CKD

TABLE 3. Relative Risks for Chronic Kidney Disease Associated with Lifestyle Behaviors and Obesity

N = 9082

	Model 1†		Model 2‡		Model 3§	
	RR	95% CI	RR	95% CI	RR	95% CI
Physical activity						
High*	1.0		1.0		1.0	
Moderate	1.2	0.7–1.8	1.1	0.7–1.7	1.2	0.7–2.0
Low	2.2	1.3–3.8	1.8	1.0–3.3	2.2	1.2–4.1
Smoking						
Never*	1.0		1.0		1.0	
Former	0.9	0.6–1.3	0.9	0.6–1.4	0.8	0.5–1.2
Current						
1–20 cigarettes/day	1.2	0.7–2.3	1.4	0.7–2.7	0.9	0.5–1.9
> 20 cigarettes/day	2.3	1.3–4.2	2.3	1.2–4.3	2.6	1.4–4.7
Alcohol consumption						
Never*	1.0		1.0		1.0	
Seldom	0.7	0.4–1.2	0.8	0.4–1.4	0.5	0.3–1.0
Weekly	0.7	0.5–1.1	0.9	0.6–1.3	0.9	0.6–1.3
Daily	0.9	0.5–1.5	0.9	0.5–1.6	0.9	0.4–2.2
Body mass index (kg/m^2)						
Thin (<18.5)	1.3	0.5–3.1	1.6	0.7–3.9	1.0	0.2–3.8
Normal (18.5–24)*	1.0		1.0		1.0	
Overweight (25–29)	0.9	0.5–1.5	0.7	0.4–1.3	0.7	0.4–1.3
Obese (30–34)	1.0	0.6–1.8	0.7	0.4–1.3	0.7	0.4–1.4
Morbid obesity (≥ 35)	2.3	1.1–4.9	1.3	0.6–2.9	1.7	0.6–4.5

CKD definition:

1. ESRD

2. Death related to CKD

Epidemiology. 2003;14:479-87

Risk of ESRD by Amount of Leisure-Time Physical Activity

N = 245,639 Taiwanese, health checkup participants, average eGFR 91.3

MET-hr	Physical activity	No.	Person-years	No. of ESRD	HR1[b]	(95% CI)	HR2[c]	(95% CI)	HR3[d]	(95% CI)
<3.75	No reported LTPA	245,639	3,297,765	1336	1.00		1.00		1.00	
3.75-7.49	Low	122,437	1,457,626	467	0.85	(0.76-0.95)	0.93	(0.83-1.05)	0.93	(0.82-1.04)
7.5-16.49	Medium	70,818	880,996	401	0.79	(0.70-0.89)	0.87	(0.77-0.99)	0.94	(0.83-1.07)
16.5-25.49	High	27,299	378,841	222	0.74	(0.63-0.86)	0.81	(0.69-0.95)	0.87	(0.74-1.02)
>= 25.5	Very high	16,342	228,315	94	0.57	(0.45-0.71)	0.68	(0.53-0.85)	0.72	(0.57-0.91)
	P for trend				<.001		<.001		.003	
	Medium or above	114,459	1,488,152	717	0.74	(0.67-0.82)	0.82	(0.74-0.91)	0.88	(0.80-0.98)

[a]ESRD, end-stage renal disease; HR, hazard ratio; LTPA, leisure-time physical activity.
[b]HR1 adjusted for age and sex.
[c]HR2 adjusted for age, sex, education, occupational activity, smoking status, drinking status, body mass index, diabetes, hypertension, hyperlipidemia, history of cardiovascular diseases, history of cancer, long-term use of herbal medicine, and long-term use of pain medications.
[d]HR3 additionally adjusted for estimated glomerular filtration rate and proteinuria.

Mayo Clin Proc2022;97(5):881-893

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Muscle-Kidney crosstalk

Role of **secretome** in kidney regeneration/growth

www.jasn.org | EDITORIALS

Can Muscle-Kidney Crosstalk Slow Progression of CKD?

Helbert Rondon-Berrios,* Yanlin Wang,† and William E. Mitch†

*Renal-Electrolyte Division, Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; and †Nephrology Division, Department of Medicine, Baylor College of Medicine, Houston, Texas

J Am Soc Nephrol 25: 2681–2683, 2014.
doi: 10.1681/ASN.2014060566

The skeletal muscle secretome: an emerging player in muscle–bone crosstalk

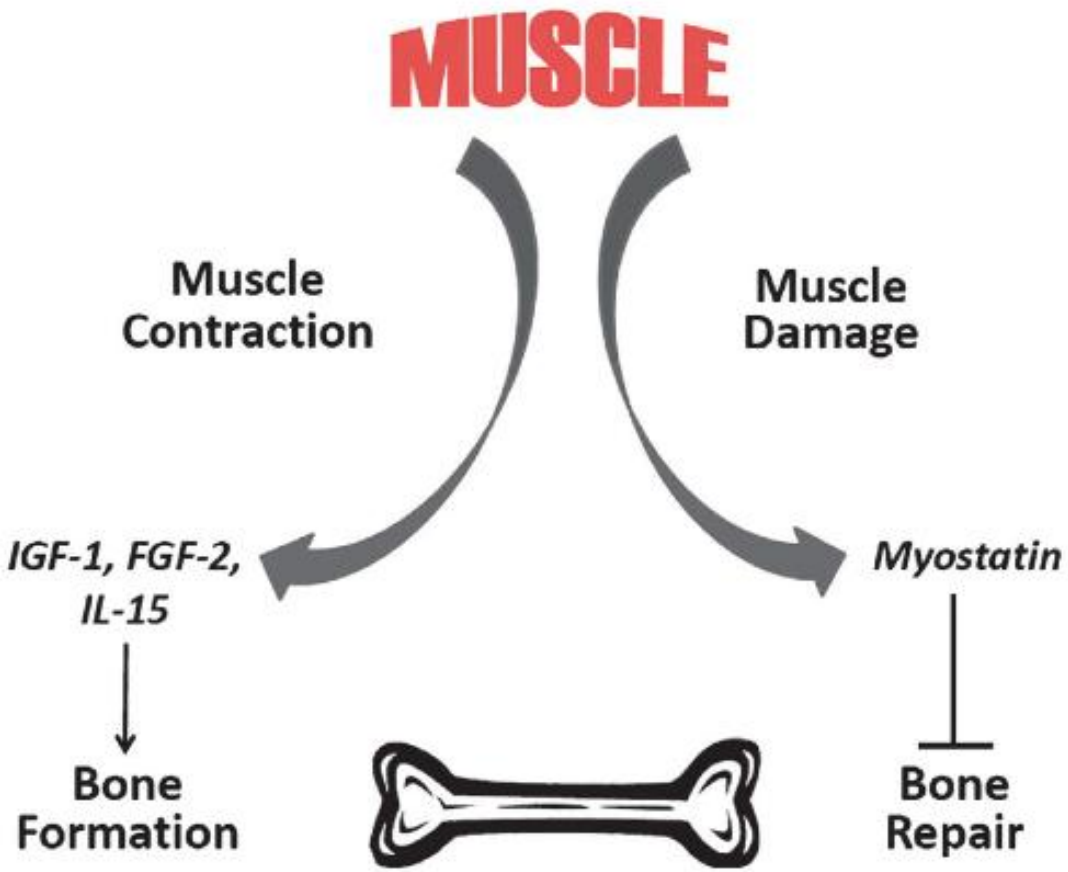


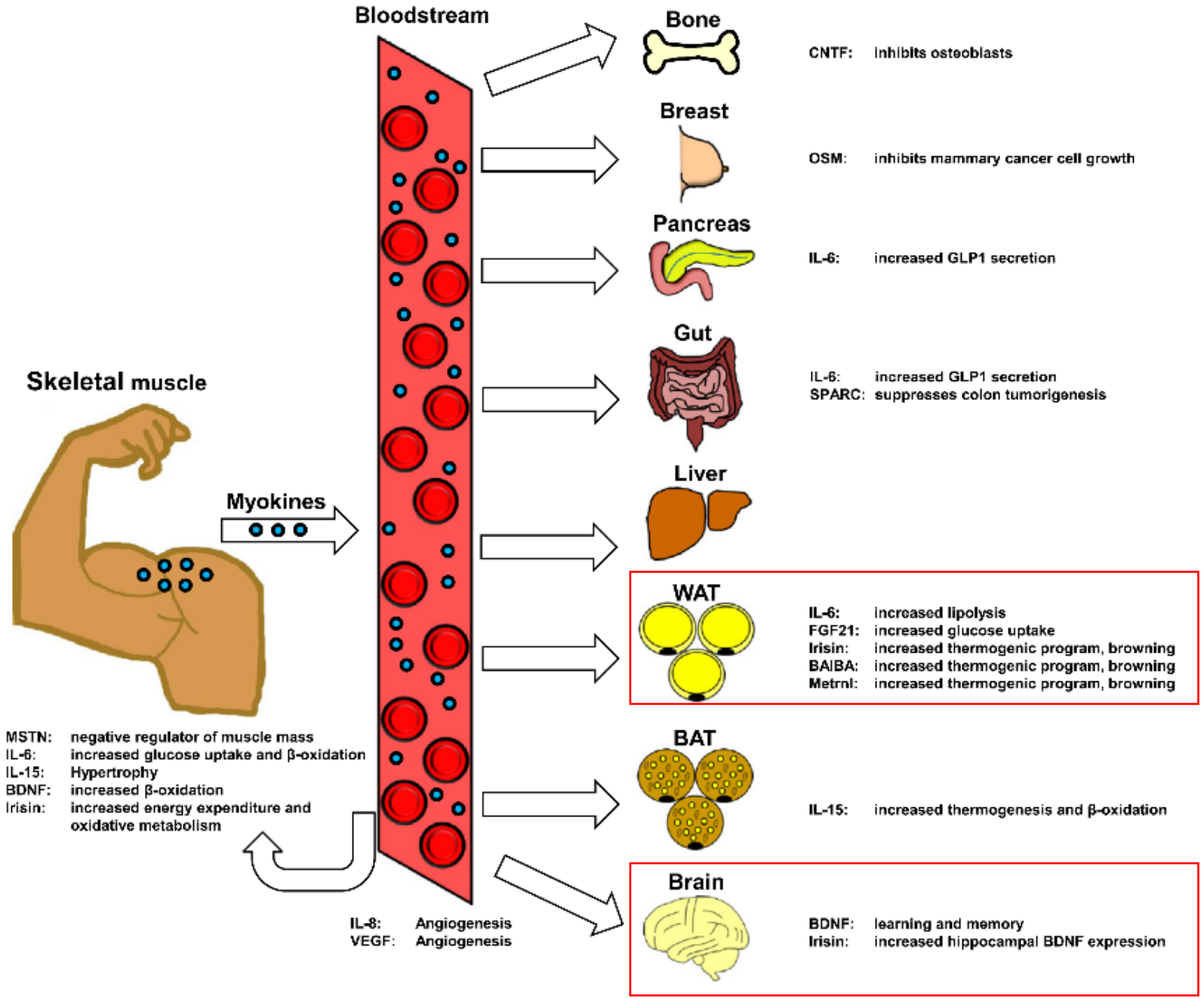
Table 1 Growth factors, cytokines and other peptides secreted by muscle, the factors that influence their secretion and their potential effects on bone metabolism

Muscle-derived peptides	*Factors that stimulate peptide secretion*	*Role(s) in bone metabolism*
Growth factors		
IGF-1	Resistance exercise	Stimulates bone formation
FGF-2	Eccentric muscle contraction	Stimulates bone formation
GDF-8	Muscle damage, cachexia, atrophy	Suppresses chondrogenesis and fracture healing
Extracellular matrix molecules		
SPARC	Resistance exercise, muscle regeneration	Promotes bone mineralization
MMP-2	Resistance exercise and re-loading	Fracture callus remodeling, bone formation
BMP-1	Blast trauma to muscle	Cleaving of procollagen and possibly heterotopic ossification
Inflammatory cytokines		
IL-6	Physical activity and muscle contraction	Bone resorption and turnover
IL-7	Physical activity and muscle contraction	Bone resorption
IL-15	Resistance exercise	Increase bone mass, decrease adiposity

Abbreviation: IL, interleukin.

Bonekey Rep 2012, 1: 60

Skeletal Muscle: a gene regulatory endocrine organ

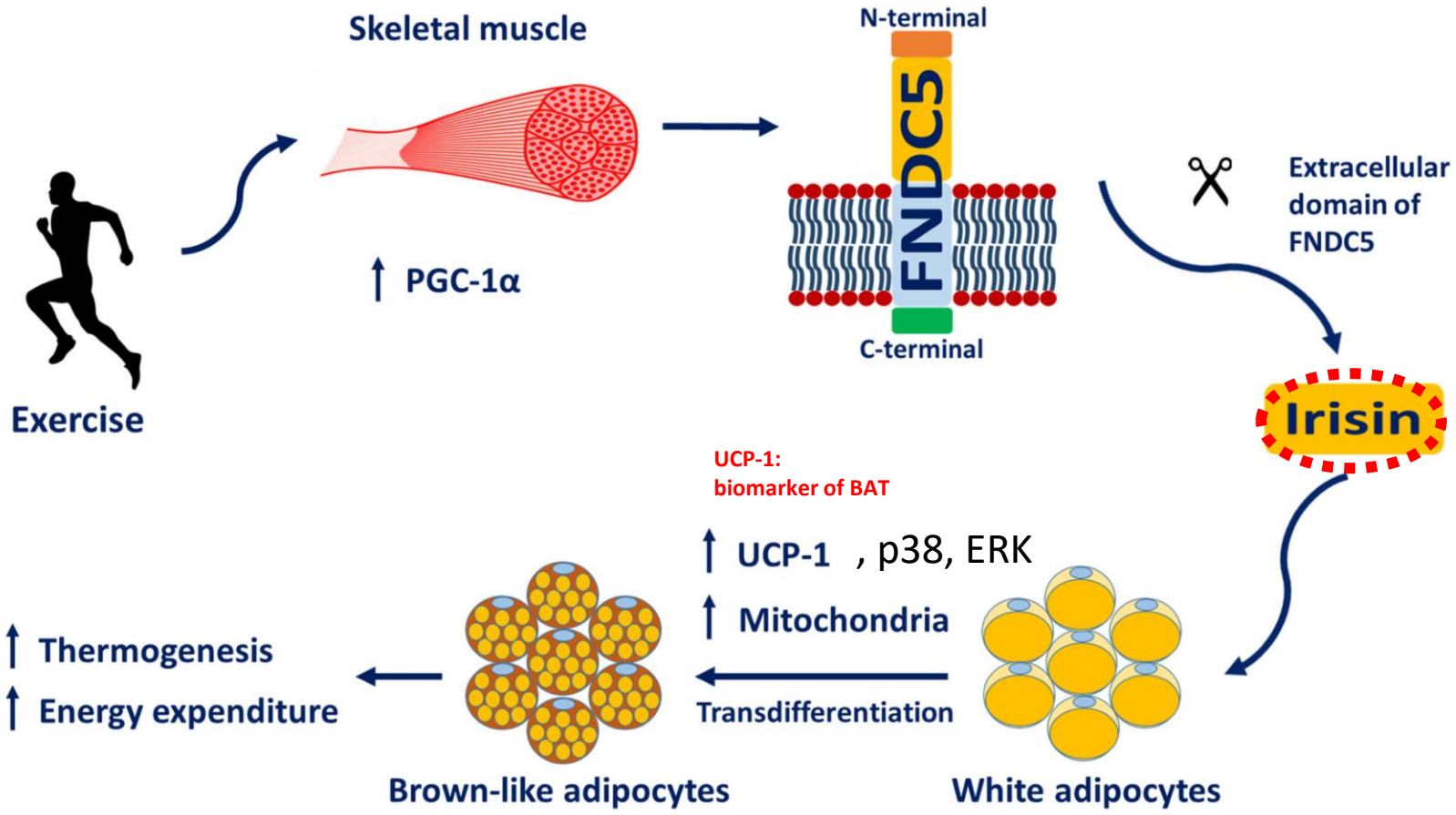


Bone. 2015;80:115-125

Exercise increases PGC-1α and Irisin

Iris

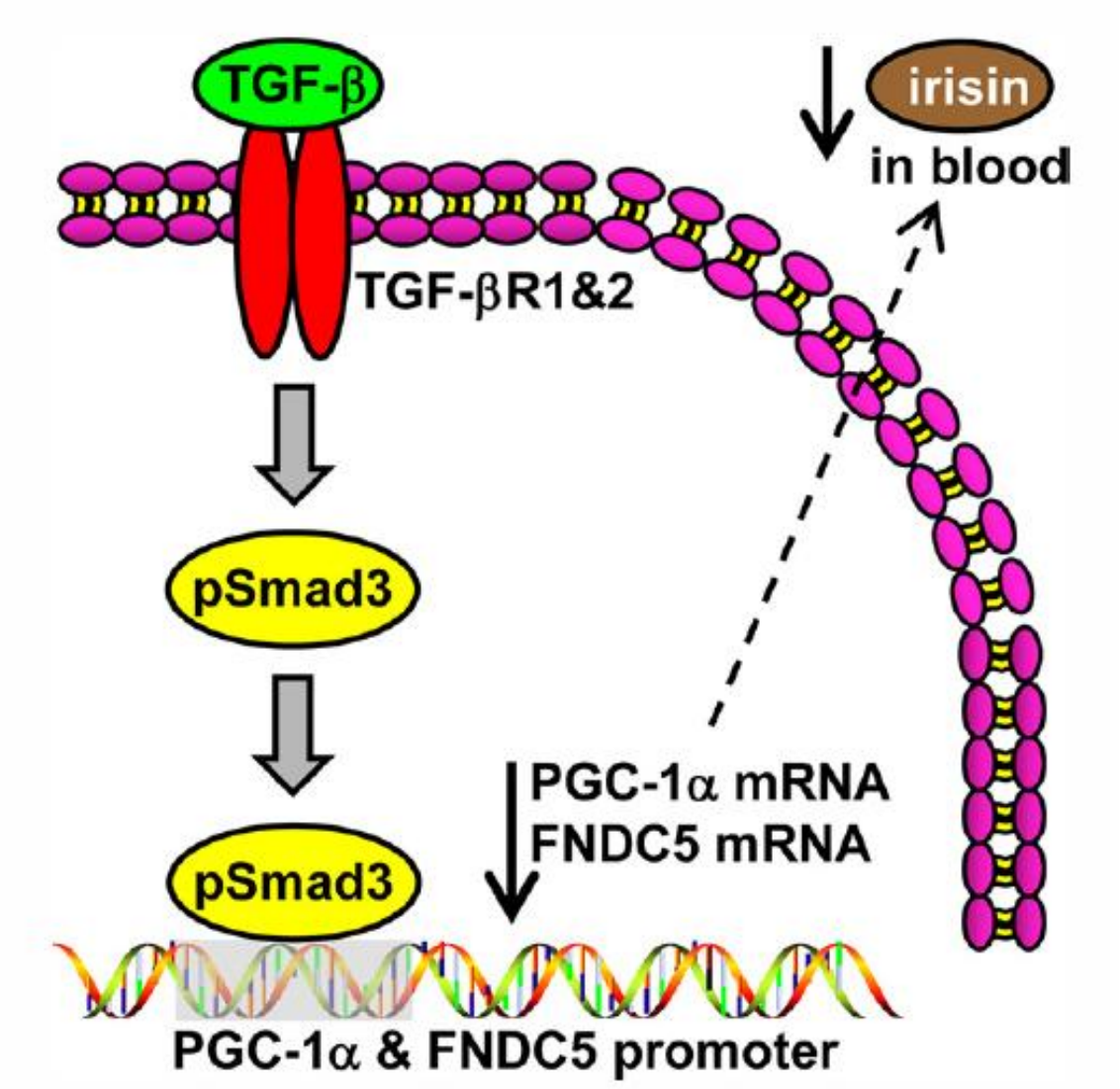
Messenger who delivered news from the gods

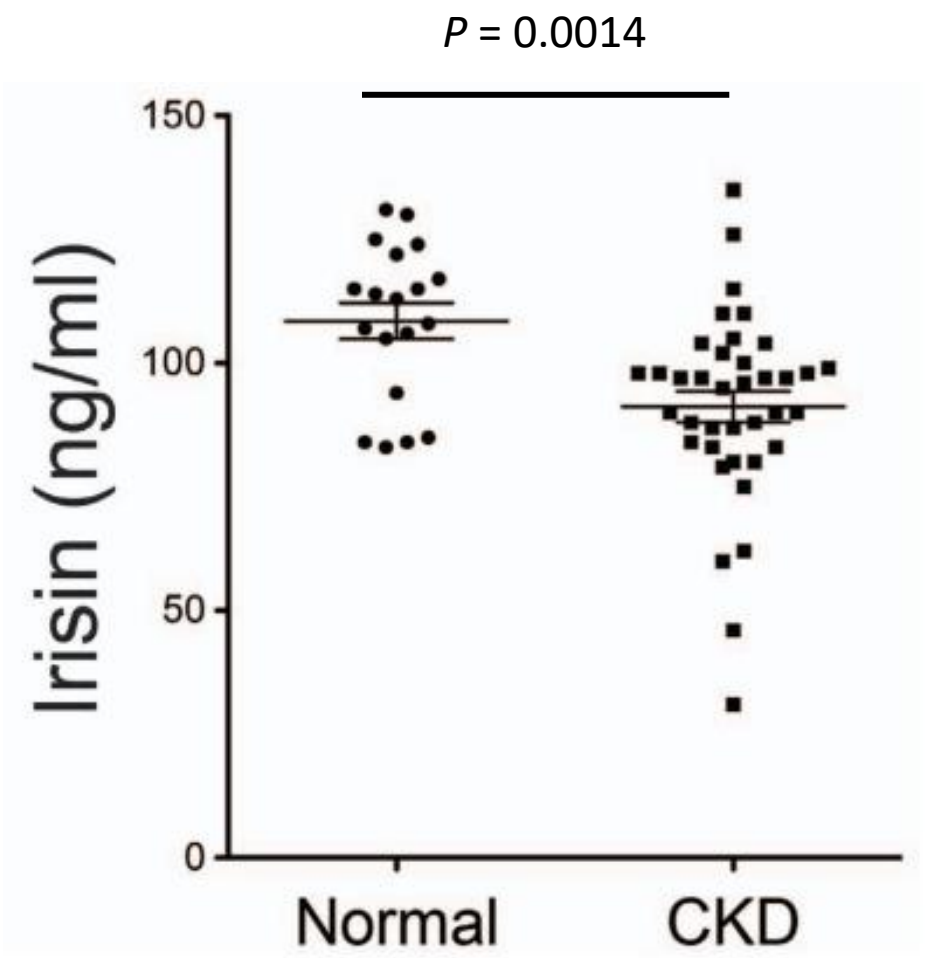


PGC-1α: peroxisome proliferator-activated receptor gamma coactivator-1α; FNDC5: fibronectin type III domain containing 5; UCP-1: uncoupling protein-1.

Eat Weight Disord.2018;23:431-42
Diabetes.2014;63:381-3
Cell Metab.2012;15:277-8

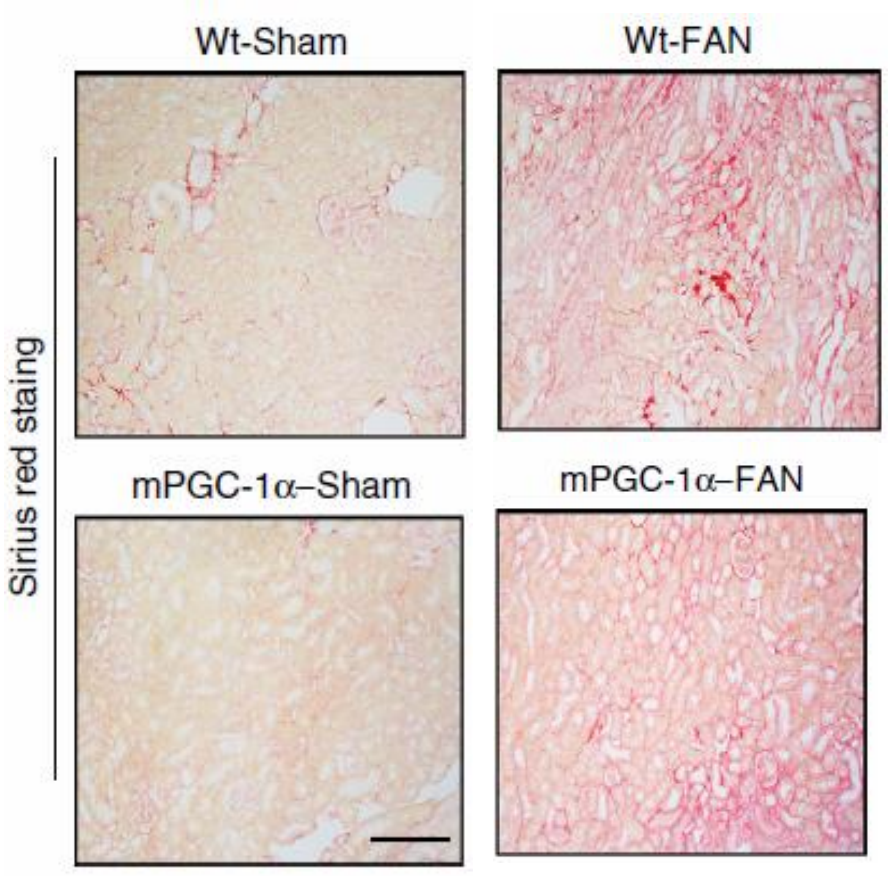
Smad3 negatively regulates PGC-1α and serum irisin

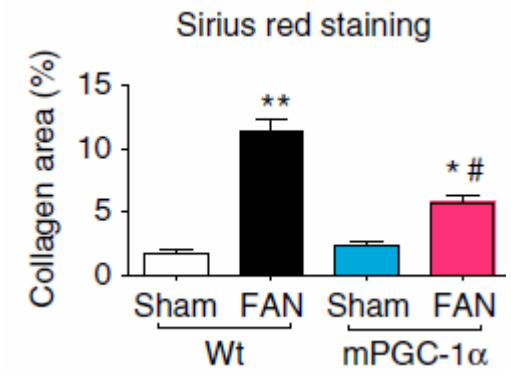


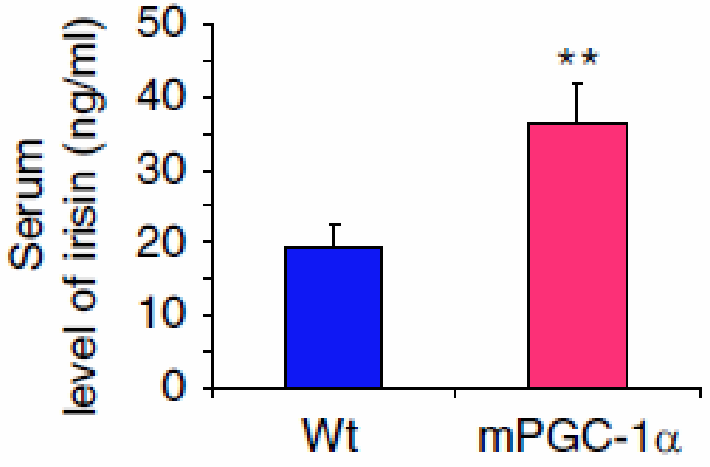


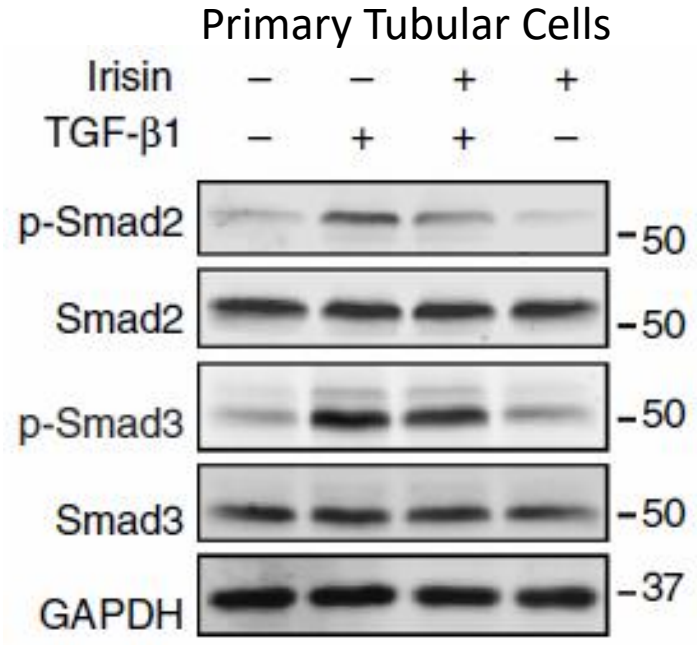
J Biol Chem. 2015;290:7671-8
PLoS One. 2013 May 7;8(5):e64025.

Muscle-specific PGC-1α overexpression ↓ renal fibrosis









Nat Commun. 2017 Nov 14;8(1):1493.

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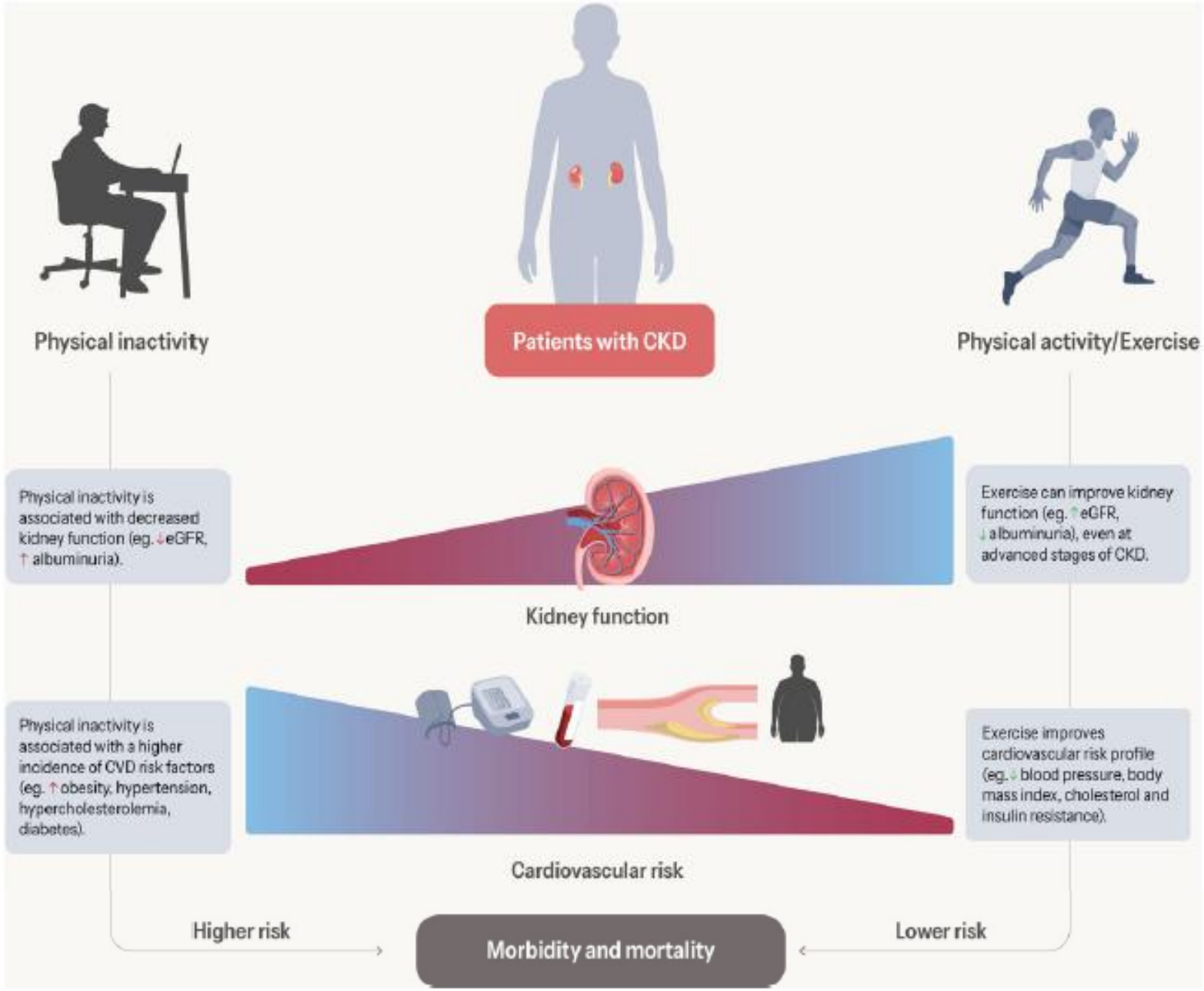
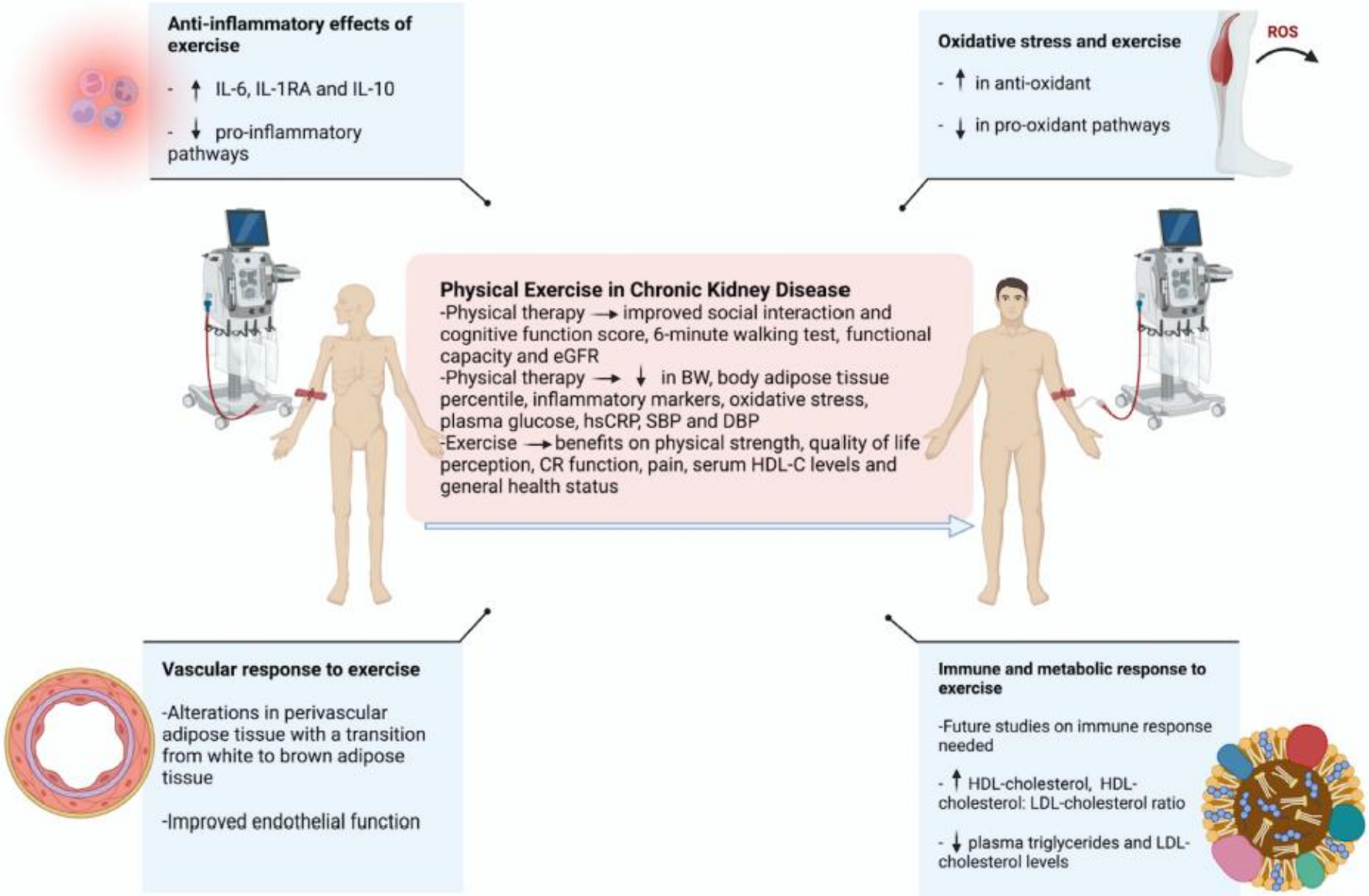


Nephrol Dial Transplant. 2024;39:1384-1391.

PA on inflammation, ROS, metabolism and vascular functions in CKD



Eur J Clin Invest. 2024;54:e14105

Effects of PA on outcome in real-world CKD patients

Physical Activity and Mortality in Chronic Kidney Disease (NHANES III)

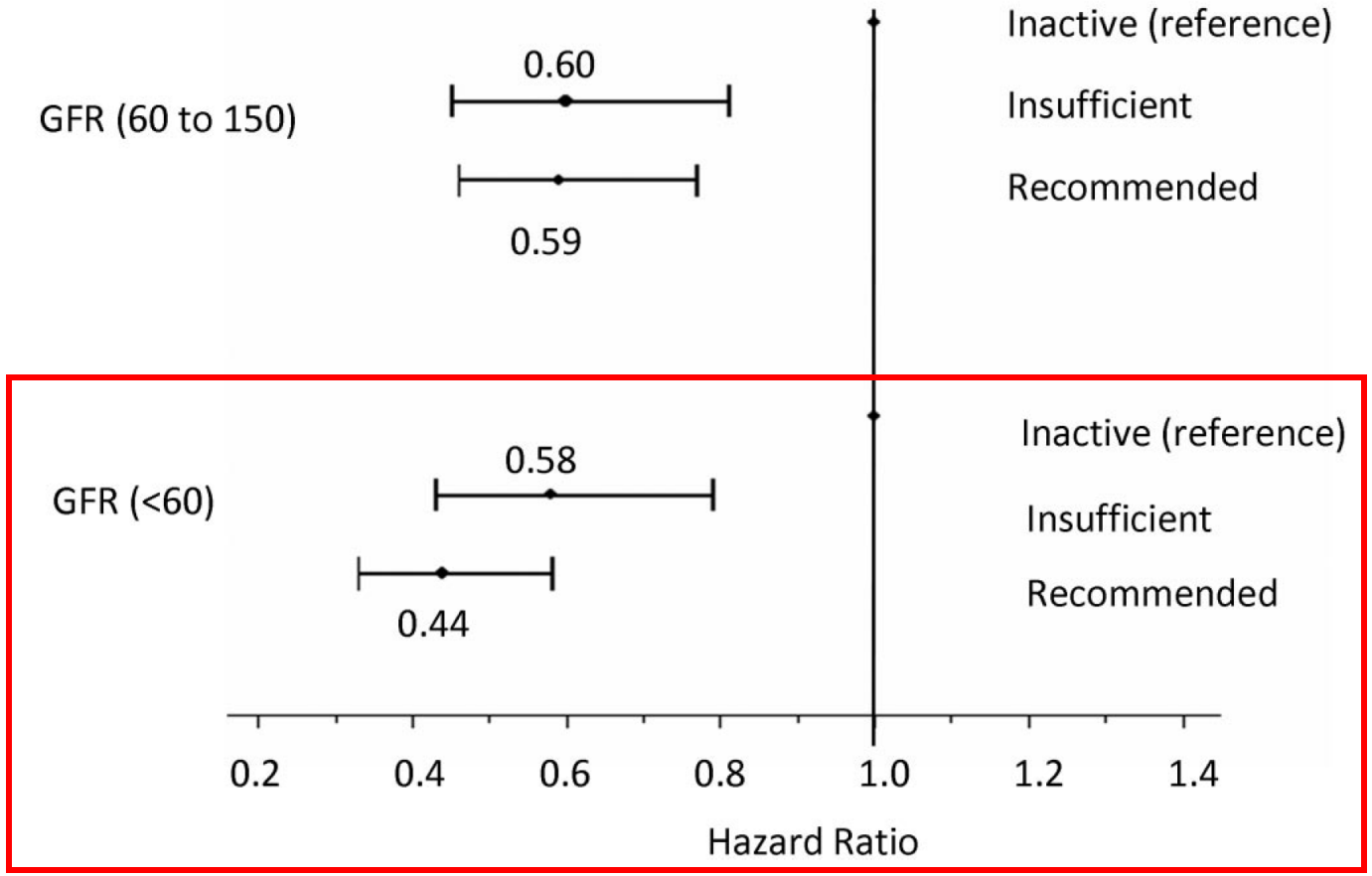
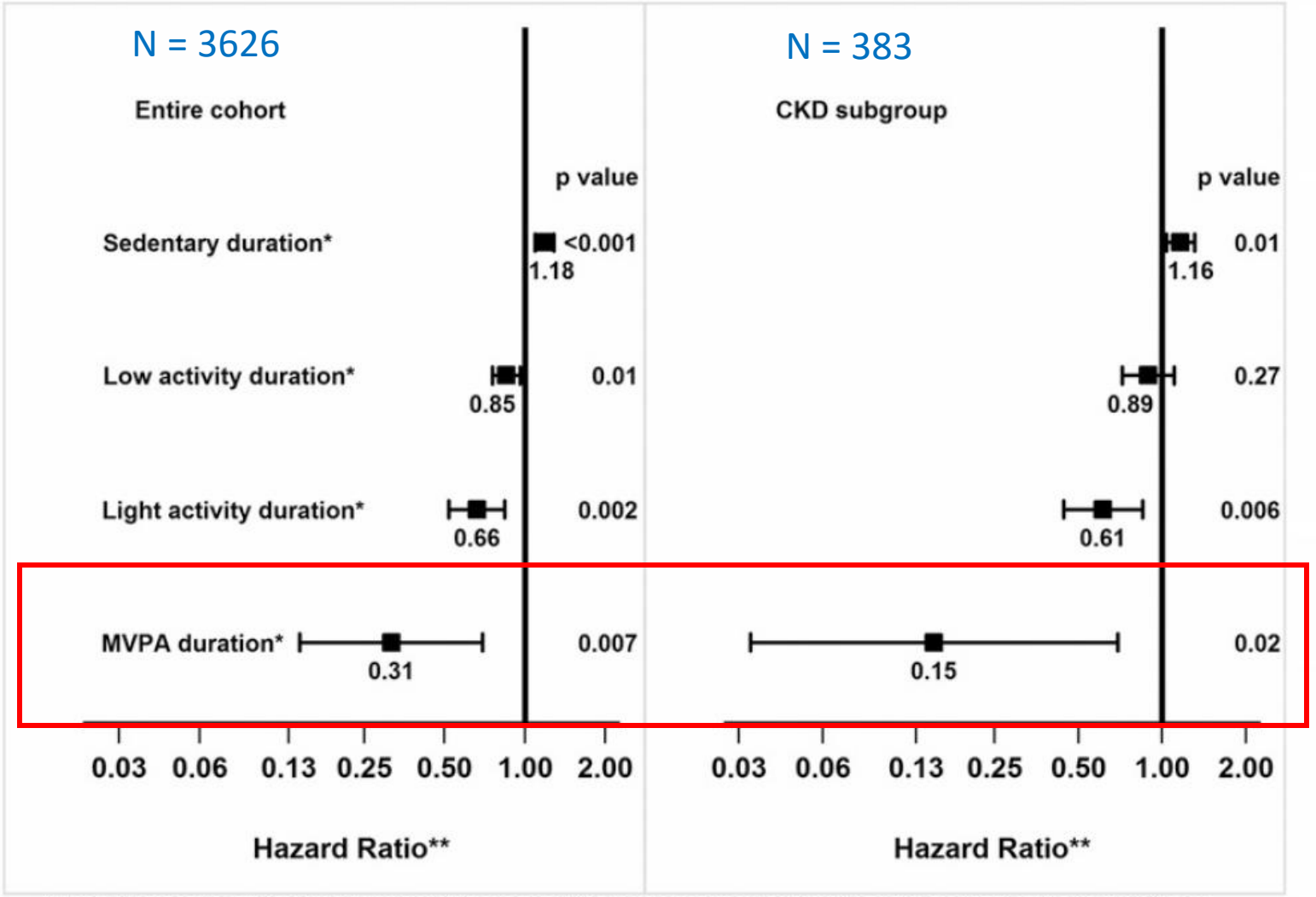


Figure 1. Associations of physical activity with mortality in non-CKD and CKD subpopulations in NHANES III.

Clin J Am Soc Nephrol . 2009 Dec;4(12):1901-6

Association between Physical activity by Accelerometer and Mortality

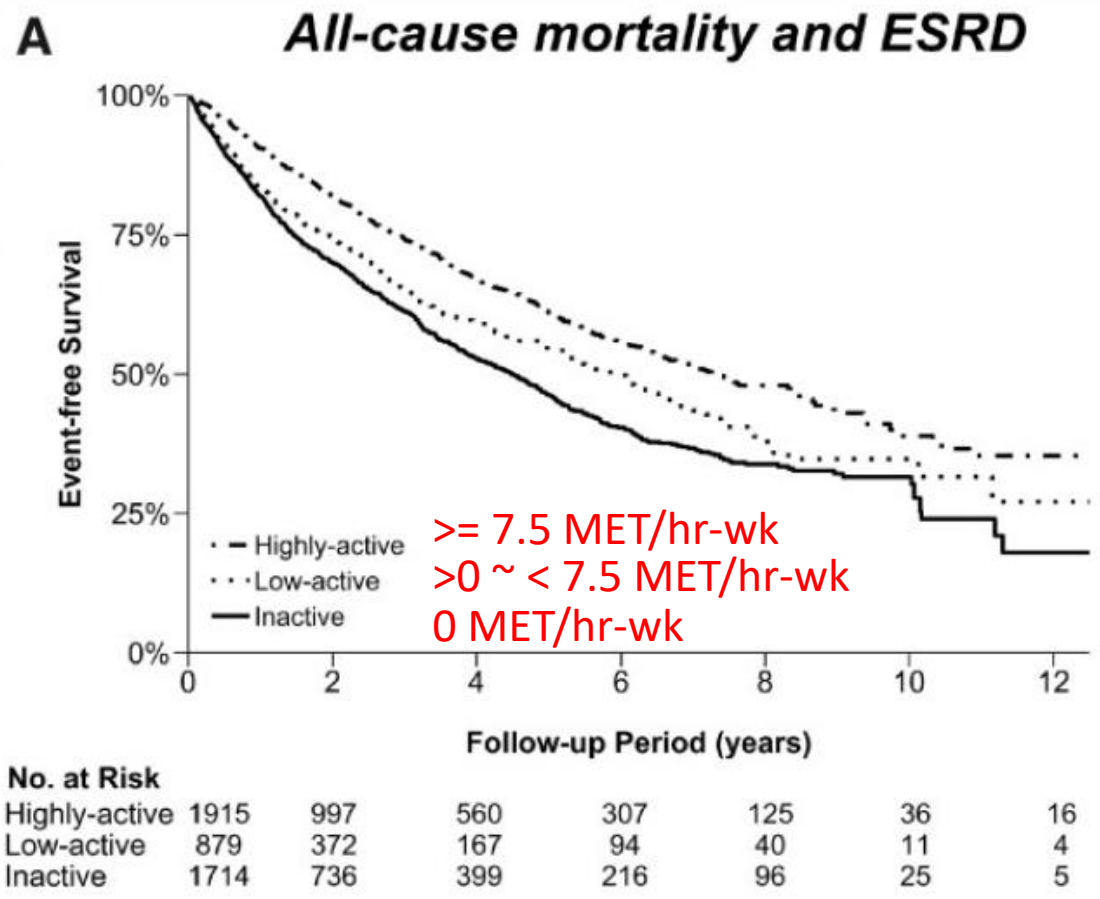


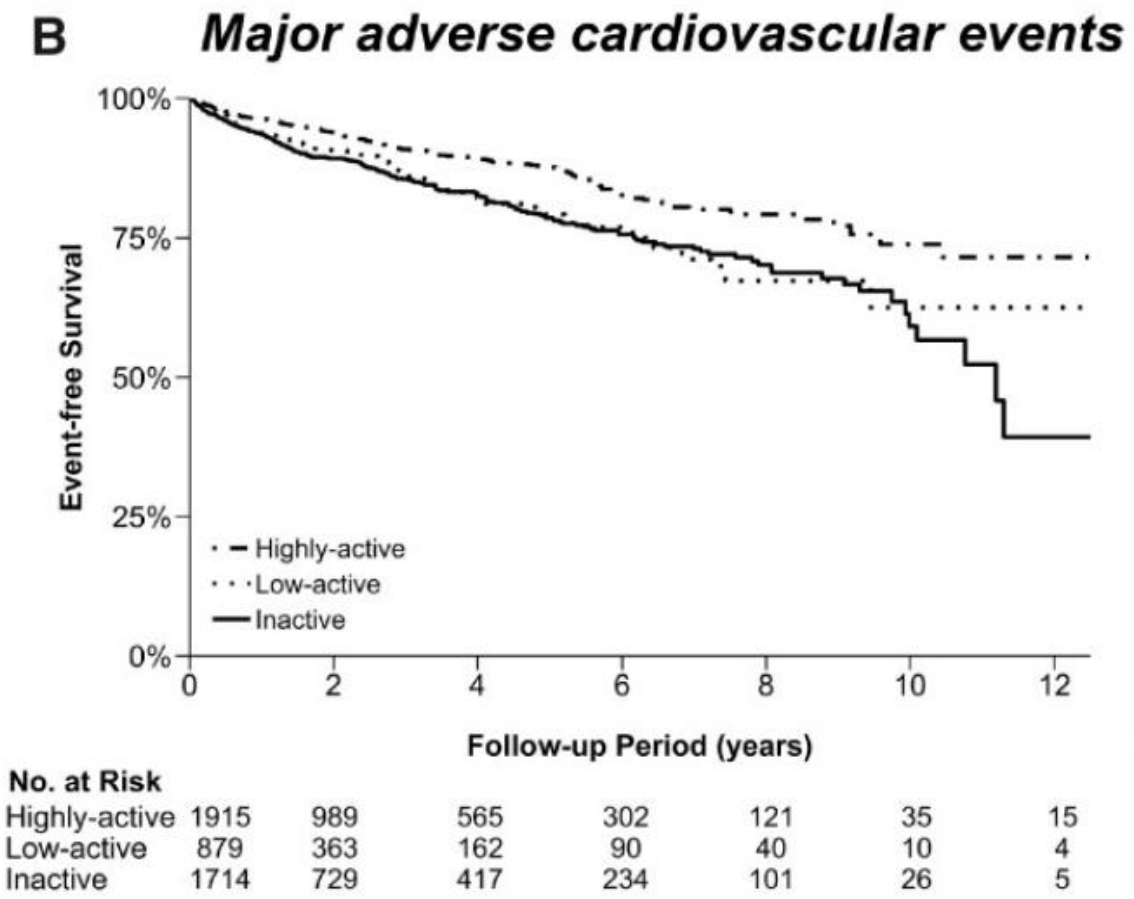
*Each line represents 2 min/hr more in a seperate model without adjustment for other activity durations
**Adjusted for age, gender, race, education, smoking, alcohol use, lung disease and mobility limitations

Clin J Am Soc Nephrol . 2015 Jul 7;10(7):1145-53

Dose–response effects of physical activity on major adverse cardiorenal outcomes in CKD

N = 4508 CKD (eGFR < 45 or UPCR >= 1 g/g)
Physical activity assessed by the NHANES questionnaire





Kuo CP, ..., Tseng WC*, Tarng DC*. Eur J Prev Cardiol. 2022 Mar 25;29(3):452-461.

Dose–response effects of physical activity on major adverse cardiorenal outcomes in CKD

Characteristics	Physical activity				
	Inactive (0 MET-h/week)	Low-active (0 to <7.5 MET-h/week)	*P* value	Highly active (≥7.5 MET-h/week)	*P* value
Participants, *N* (%)	1714 (38.0)	879 (19.5)		1915 (42.5)	
All-cause mortality and ESRD					
Event, *N* (%)	705 (41.1)	289 (32.9)		563 (29.4)	
Age and sex-adjusted HR (95% CI)	Reference	0.86 (0.75–0.98)	0.03	0.64 (0.57–0.71)	<0.001
Fully adjusted HR (95% CI)[a]	Reference	0.92 (0.80–1.05)	0.22	0.75 (0.67–0.84)	<0.001
All-cause mortality					
Event, *N* (%)	339 (19.8)	130 (14.8)		270 (14.1)	
Age and sex-adjusted HR (95% CI)	Reference	0.79 (0.64–0.97)	0.02	0.54 (0.46–0.64)	<0.001
Fully adjusted HR (95% CI)[a]	Reference	0.86 (0.70–1.06)	0.16	0.62 (0.53–0.74)	<0.001
ESRD					
Event, *N* (%)	486 (28.4)	196 (22.3)		377 (19.7)	
Age and sex-adjusted HR (95% CI)	Reference	0.87 (0.74–1.03)	0.10	0.68 (0.59–0.78)	<0.001
Fully adjusted HR (95% CI)[a]	Reference	0.93 (0.78–1.10)	0.38	0.83 (0.72–0.96)	0.01
MACE					
Event, *N* (%)	237 (13.8)	104 (11.8)		180 (9.4)	
Age and sex-adjusted HR (95% CI)	Reference	0.89 (0.71–1.12)	0.32	0.56 (0.46–0.67)	<0.001
Fully adjusted HR (95% CI)[a]	Reference	0.90 (0.71–1.14)	0.39	0.63 (0.51–0.76)	<0.001

Kuo CP, ..., Tseng WC*, Tarng DC*. Eur J Prev Cardiol. 2022 Mar 25;29(3):452-461.

Sustained physical activity: pivotal for best outcome

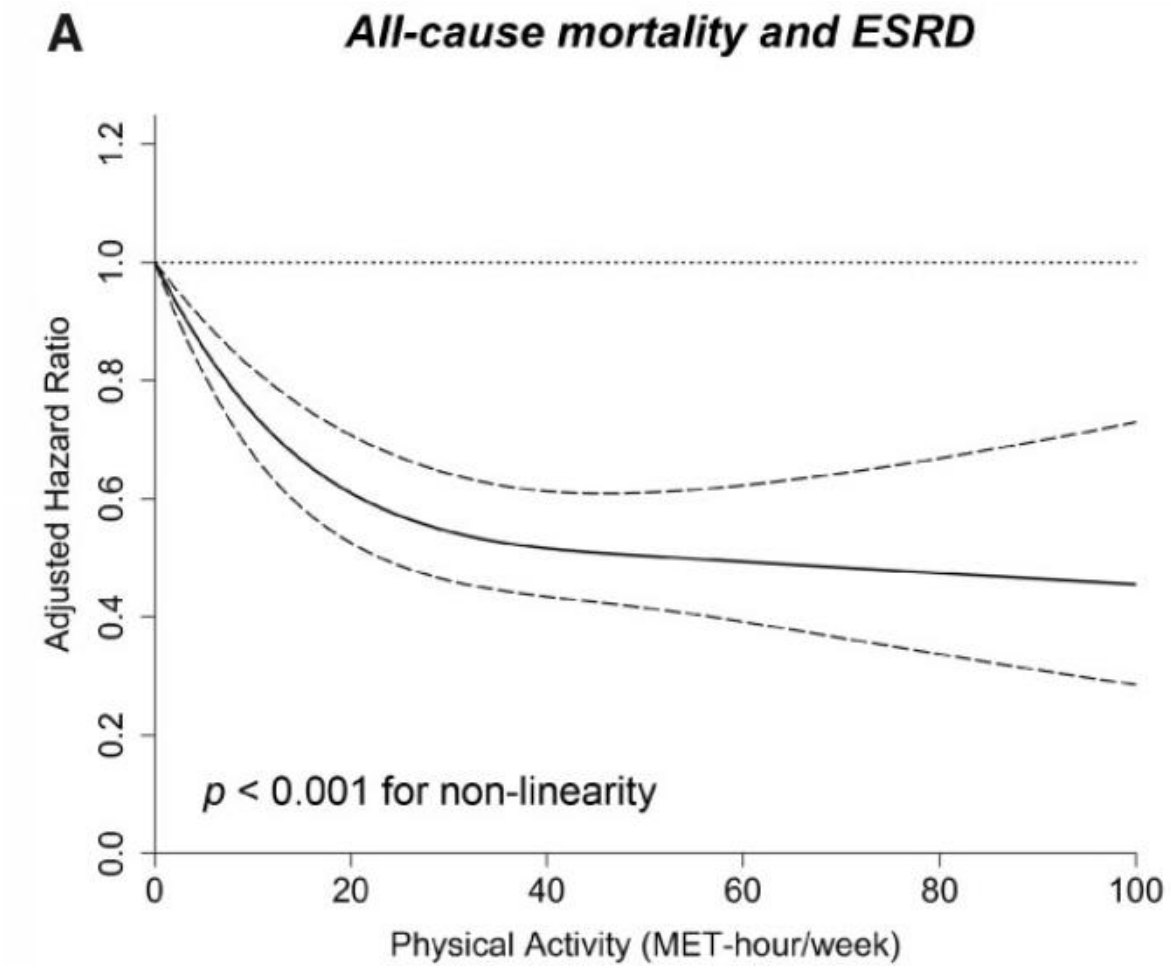
Supplemental Table S8. Changes in physical activity levels and risks for all-cause mortality, ESRD and MACE in chronic kidney disease patients

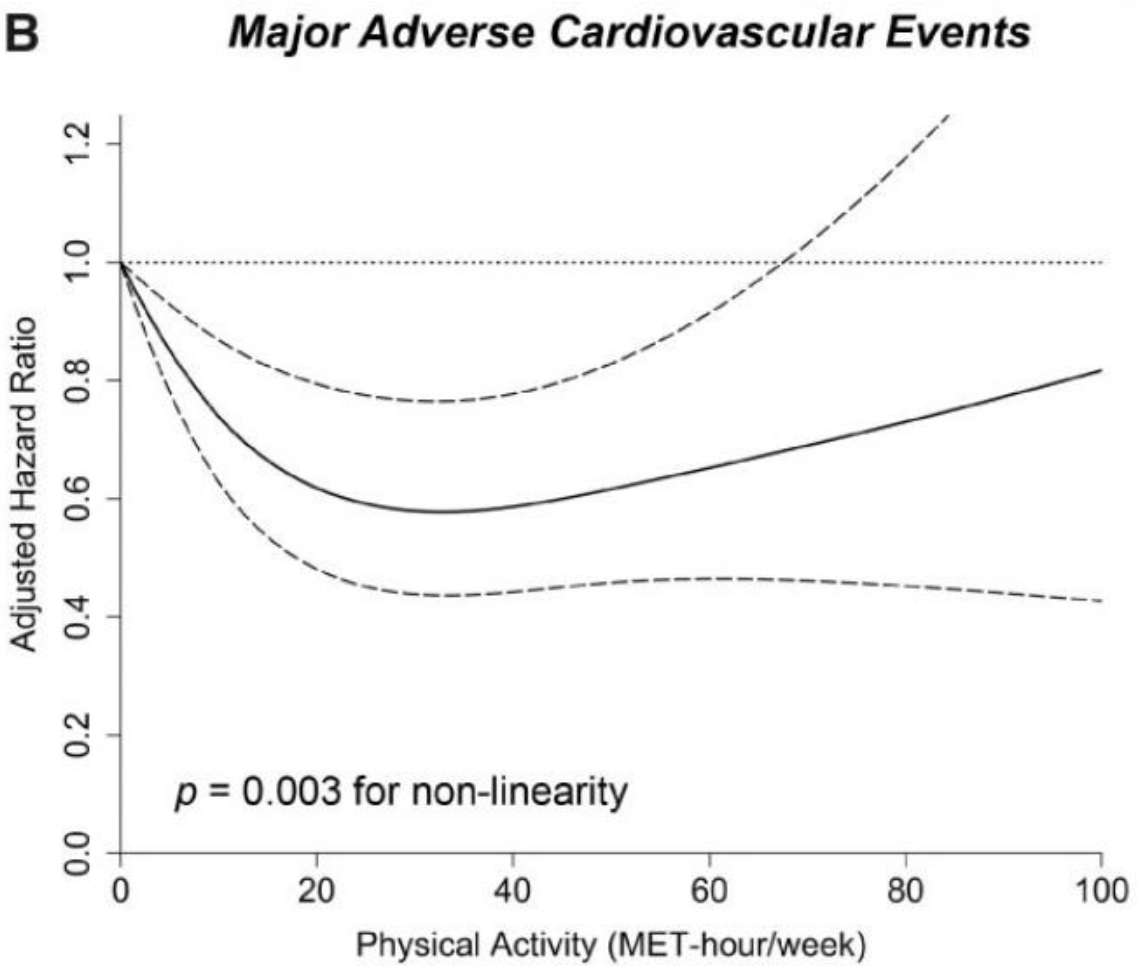
Change in Physical activity	N	All-cause mortality and ESRD			All-cause mortality			ESRD			MACE		
		E	Fully-adjusted HR (95% CI)*	*p* value	E	Fully-adjusted HR (95% CI)*	*p* value	E	Fully-adjusted HR (95% CI)*	*p* value	E	Fully-adjusted HR (95% CI)*	*p* value
Highly-Active													
Continually highly-active	1395	419	Reference		198	Reference		340	Reference		125	Reference	
Highly-active to less active#	274	66	1.39 (1.06-1.82)	0.017	44	2.20 (1.55-3.13)	<0.001	1	1.21 (0.84-1.75)	0.31	41	2.04 (1.32-3.14)	0.001
Low-Active													
Continually low-active	586	185	Reference		99	Reference		113	Reference		75	Reference	
Low-active to highly-active	23	2	0.99 (0.23-4.23)	0.99	1	0.83 (0.10-6.77)	0.86	1	1.22 (0.16-9.54)	0.85	3	1.51 (0.31-7.27)	0.61
Low-active to inactive	94	28	1.26 (0.81-1.95)	0.31	14	1.23 (0.66-2.32)	0.52	16	1.23 (0.68-2.24)	0.49	16	0.53 (0.22-1.28)	0.16
Inactive													
Continually inactive	1362	524	Reference		270	Reference		340	Reference		196	Reference	
Inactive to more active†	23	5	1.60 (0.65-3.92)	0.31	4	2.53 (0.91-7.05)	0.08	1	0.71 (0.10-5.15)	0.73	3	2.00 (0.61-6.52)	0.25

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; E, number of events; ESRD, end-stage renal disease; HR, hazard ratio; MACE, major adverse cardiac events; N, number of total patients

Kuo CP, ..., Tseng WC*, Tarng DC*. Eur J Prev Cardiol. 2022 Mar 25;29(3):452-461.

U-shaped association between of PA and MACE in CKD





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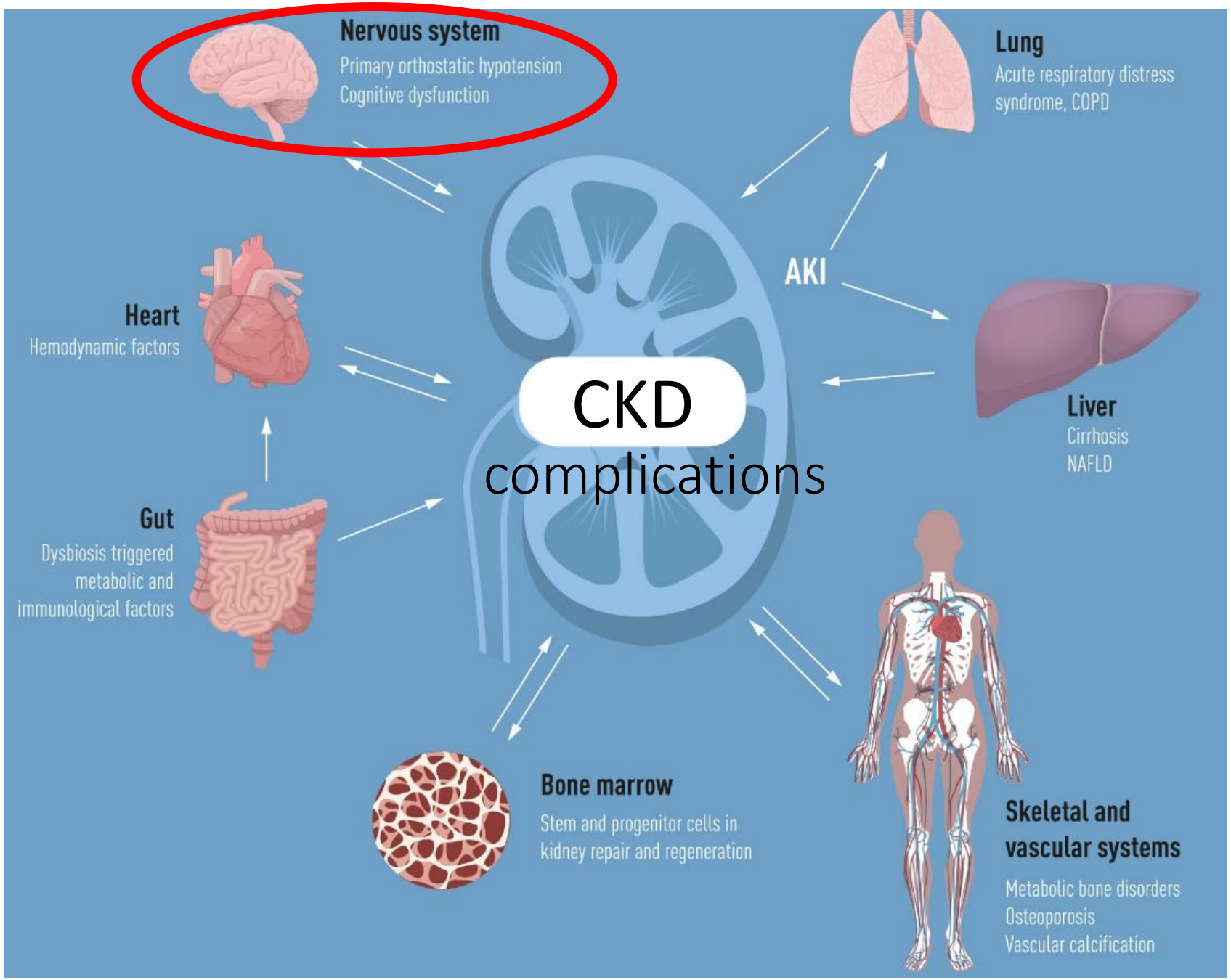
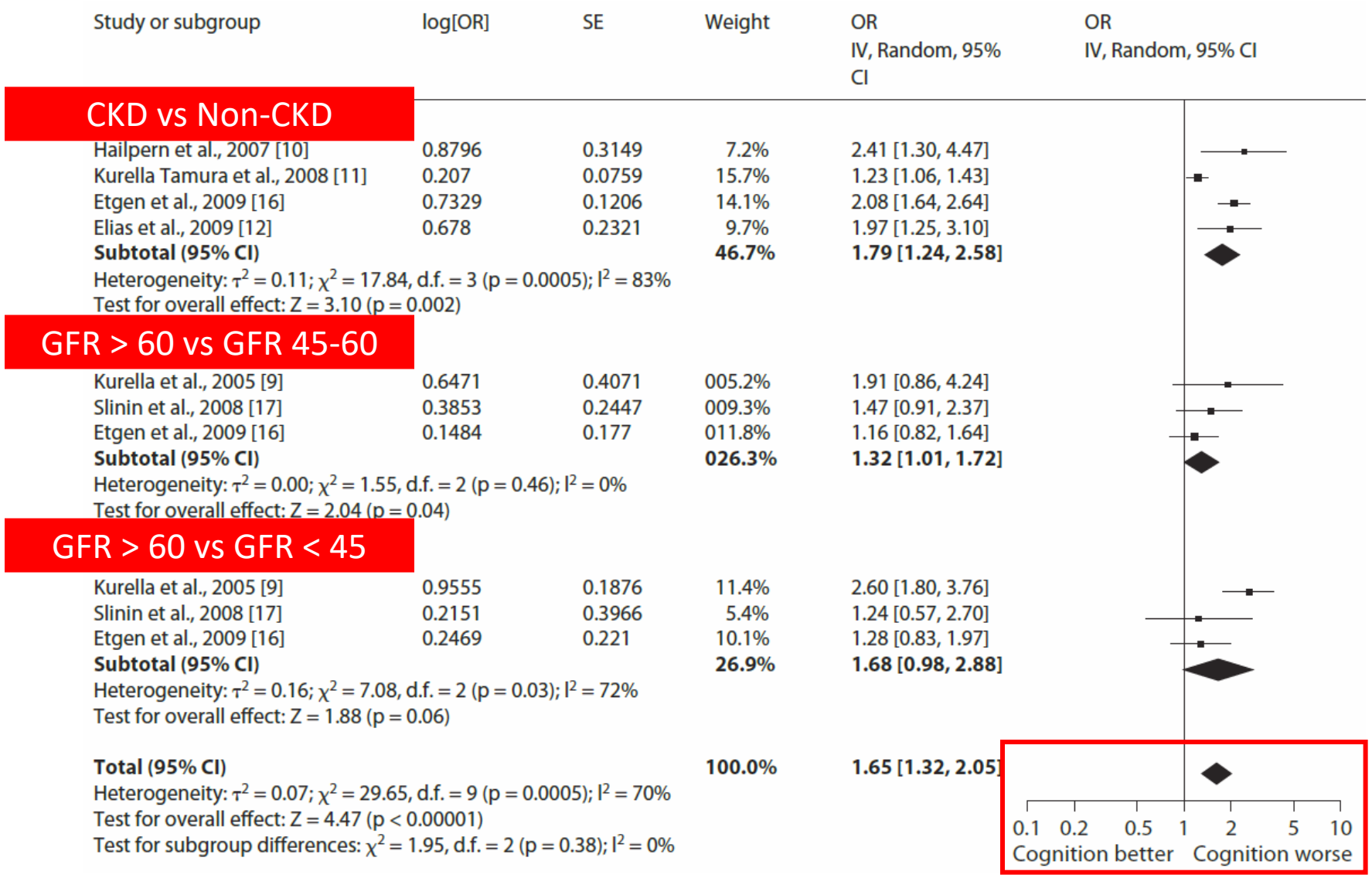


J Intern Med. 2025 Nov;298:368-391.

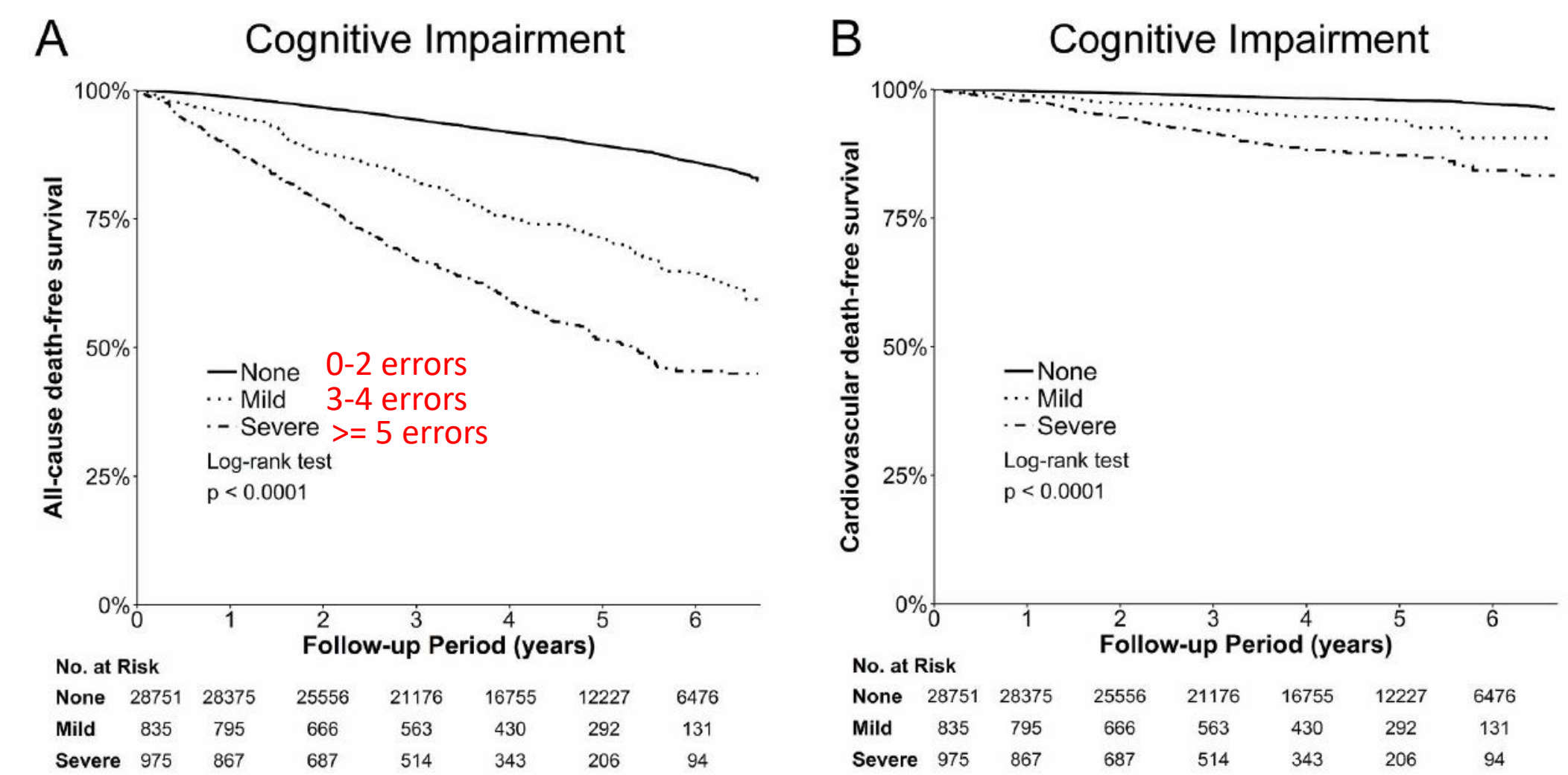
CKD and Cognitive Impairment



Am J Nephrol 2012;35:474–482

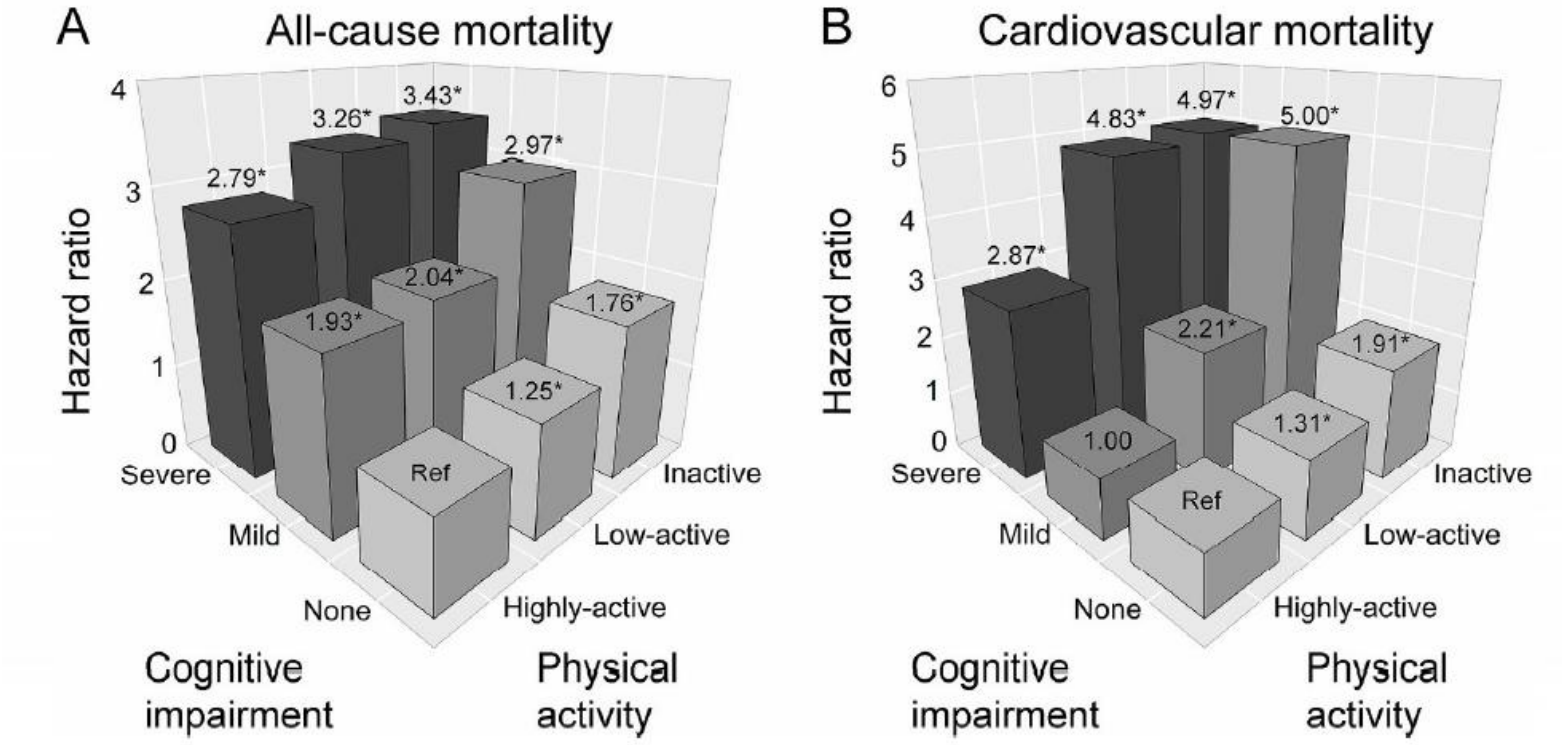
Cognitive impairment links to higher mortality in CKD

Cognition evaluated by SPMSQ (Short-portable mental-status questionnaire)



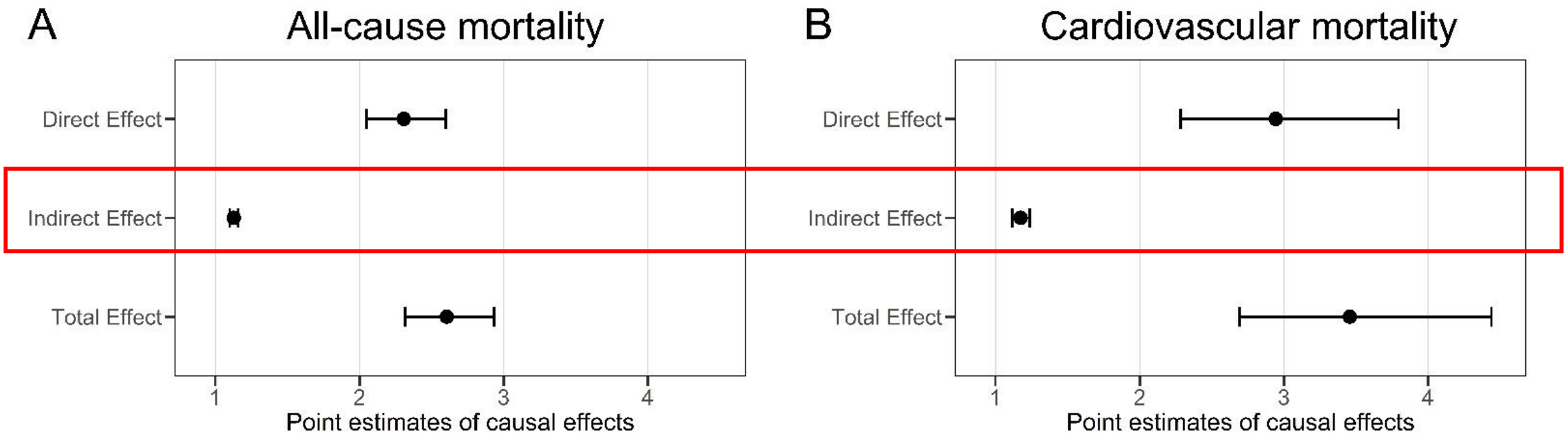
Tsai MT, ..., Tseng WC*, Tarng DC*. J Affect Disord. 2024 Dec 1:366:354-363.

Joint association between cognitive impairment and PA



Tsai MT, ..., Tseng WC*, Tarng DC*. J Affect Disord. 2024 Dec 1:366:354-363.

Mediation effects of PA in the relationship between cognitive impairment and the mortality risks



p <0.001

p <0.001

Tsai MT, ..., Tseng WC*, Tarng DC*. J Affect Disord. 2024 Dec 1:366:354-363.

Physical Activity: Protects Kidney, Heart and Brain in CKD

- Risk of physical inactivity are high both in CKD and non-CKD patients.
- Skeletal muscle-secretome (PGC-1α, Irisin) reduces renal fibrosis
- Physical activity of **7.5 to <15 MET-h/week** is associated with lower risks of adverse cardiorenal outcomes
- Extremely-high physical activity may not be feasible in CKD patients.
- Physical activity interacts with cognitive impairment on mortality in elderly CKD patients.

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