OBESITY AND CHRONIC KIDNEY DISEASE

EPIDEMIOLOGY AND CHALLENGES

Juan Jesus Carrero
Professor of Kidney Disease Epidemiology
Karolinska Institutet

DISCLOSURES

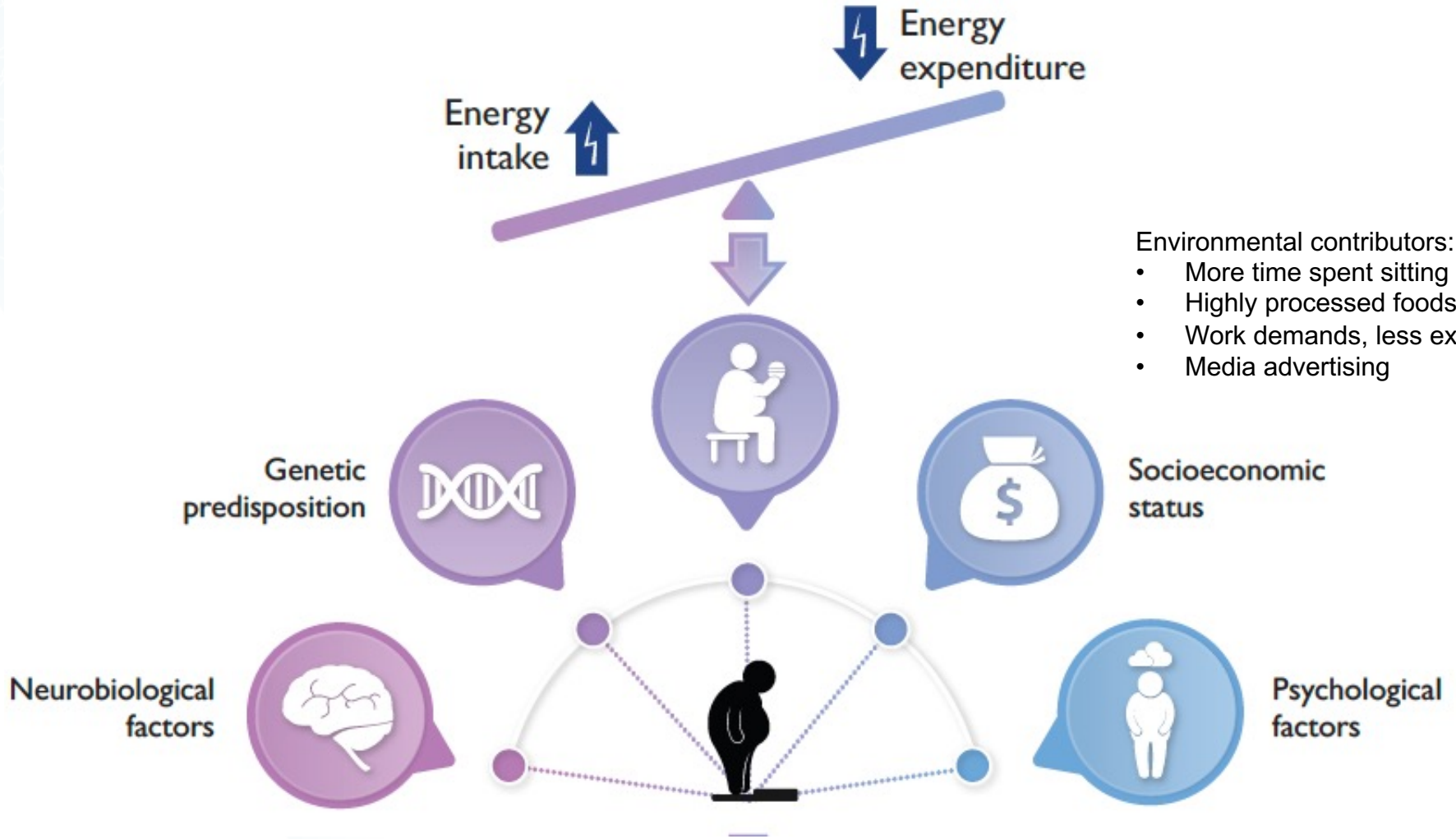
- Participation in the development of recent clinical guidelines by KDIGO, ESPEN and KDOQI
- Financial support to Karolinska Institutet from AstraZeneca, Astellas, Boehringer Ingelheim, MSD, Novordisk, ViforPharma
- Grant support to Karolinska Institutet from the Swedish Research Council, Swedish Heart and Lung Foundation, Rind and Westman Foundations, US National Institute of Health (NIH)
- Speaker or advisory board fees from Fresenius Kabi and AstraZeneca

Talk Outline (epi focus)

- Epidemic of obesity and projections
- Obesity as a risk factor for CKD
- Epidemic of CKD with obesity
- Challenges of living with CKD and obesity
- Challenges of BMI as a diagnostic tool in CKD

OVERWEIGHT AND OBESITY

abnormal or excessive fat accumulation that may impair health.



Environmental contributors:

- More time spent sitting in cars and at computers
- Highly processed foods
- Work demands, less exercise
- Media advertising

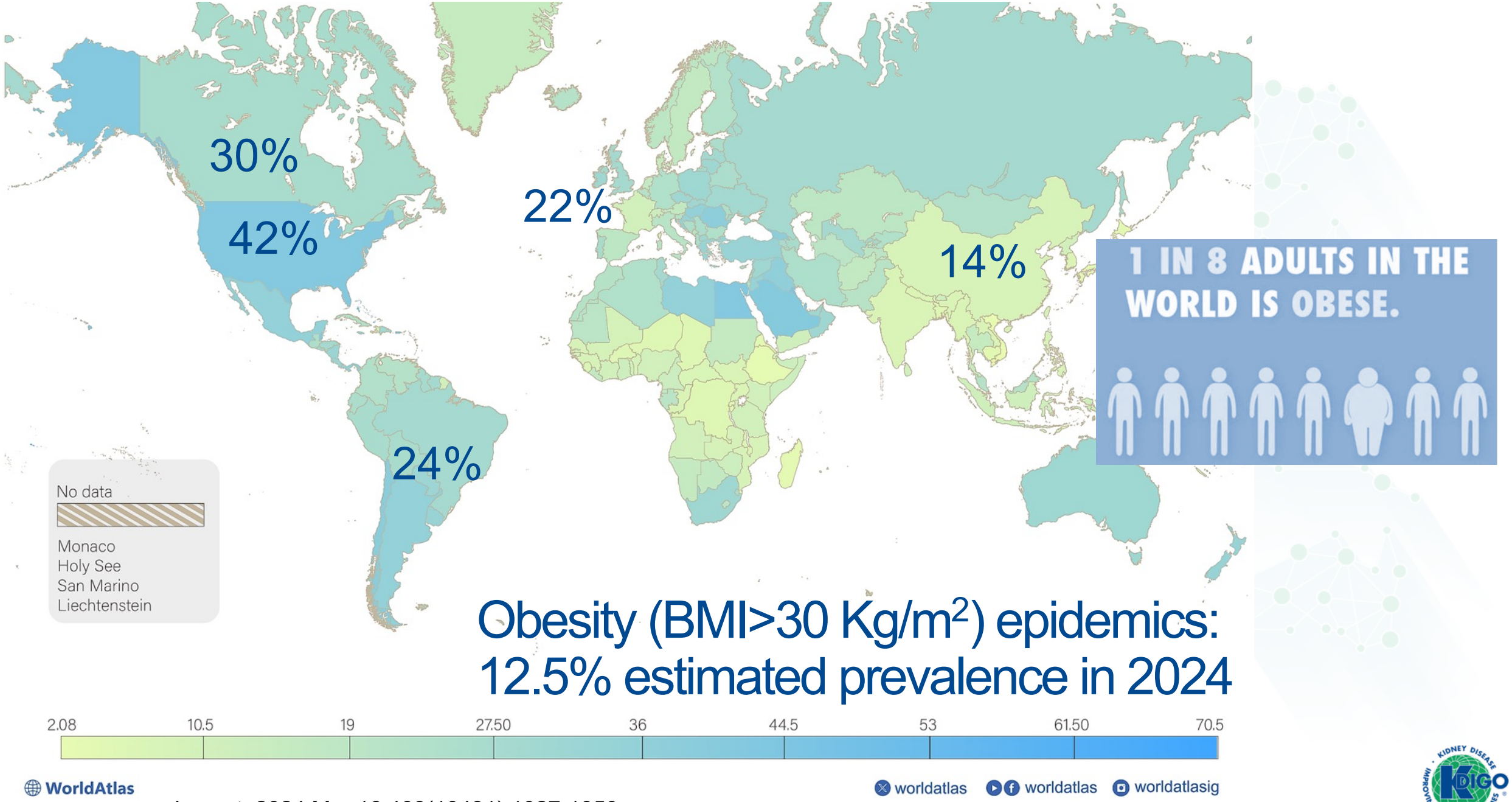
Eur Heart J. 2024 Aug 30:ehae508. doi: 10.1093/eurheartj/ehae508. Online ahead of print.

$$\text{BMI} = \frac{\text{Weight in Kg}}{[\text{Height in meters}]^2}$$

Box 1 WHO classification of overweight and obesity in adults

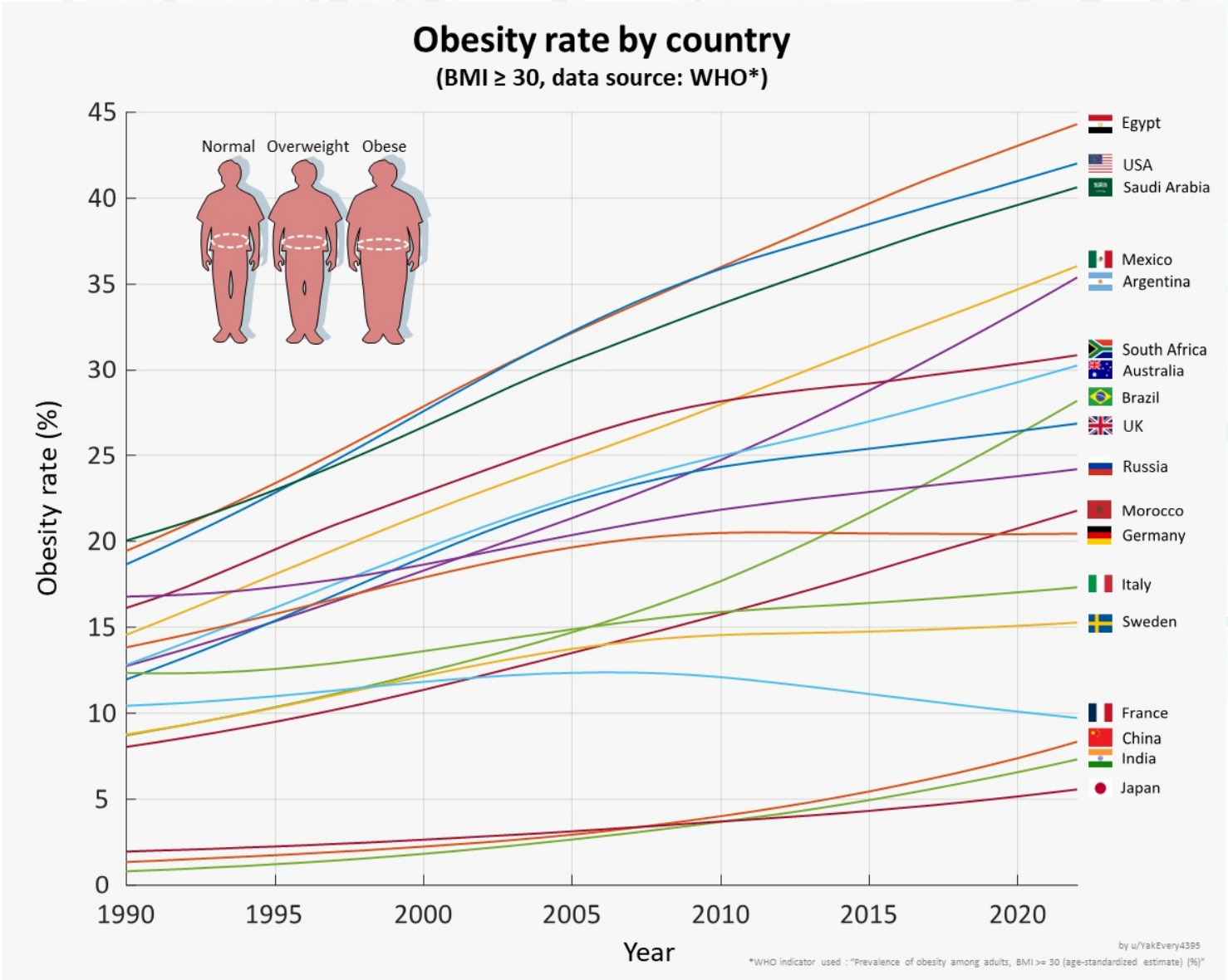
- BMI 20 to <25 kg/m^2: Normal weight
- BMI 25 to <30 kg/m^2: Overweight
- BMI ≥30 kg/m^2: Obesity
  - BMI 30 to <35 kg/m^2: Obesity Class 1
  - BMI 35 to <40 kg/m^2: Obesity Class 2
  - BMI ≥40 kg/m^2: Obesity Class 3 (severe obesity)

- **Obesity with BMI ≥35 kg/m^2 (Classes 2 and 3):** an almost entirely new phenotype from the recent decades.
- Most cases of obesity-related complications will arise from the much larger group with **overweight and Class 1 obesity**.
- **BMI** is useful for epidemiological studies, but limited as a diagnostic tool.



Lancet. 2024 Mar 16;403(10431):1027-1050.

OBESITY TRENDS: INCREASING IN (ALMOST) ALL COUNTRIES WORLDWIDE



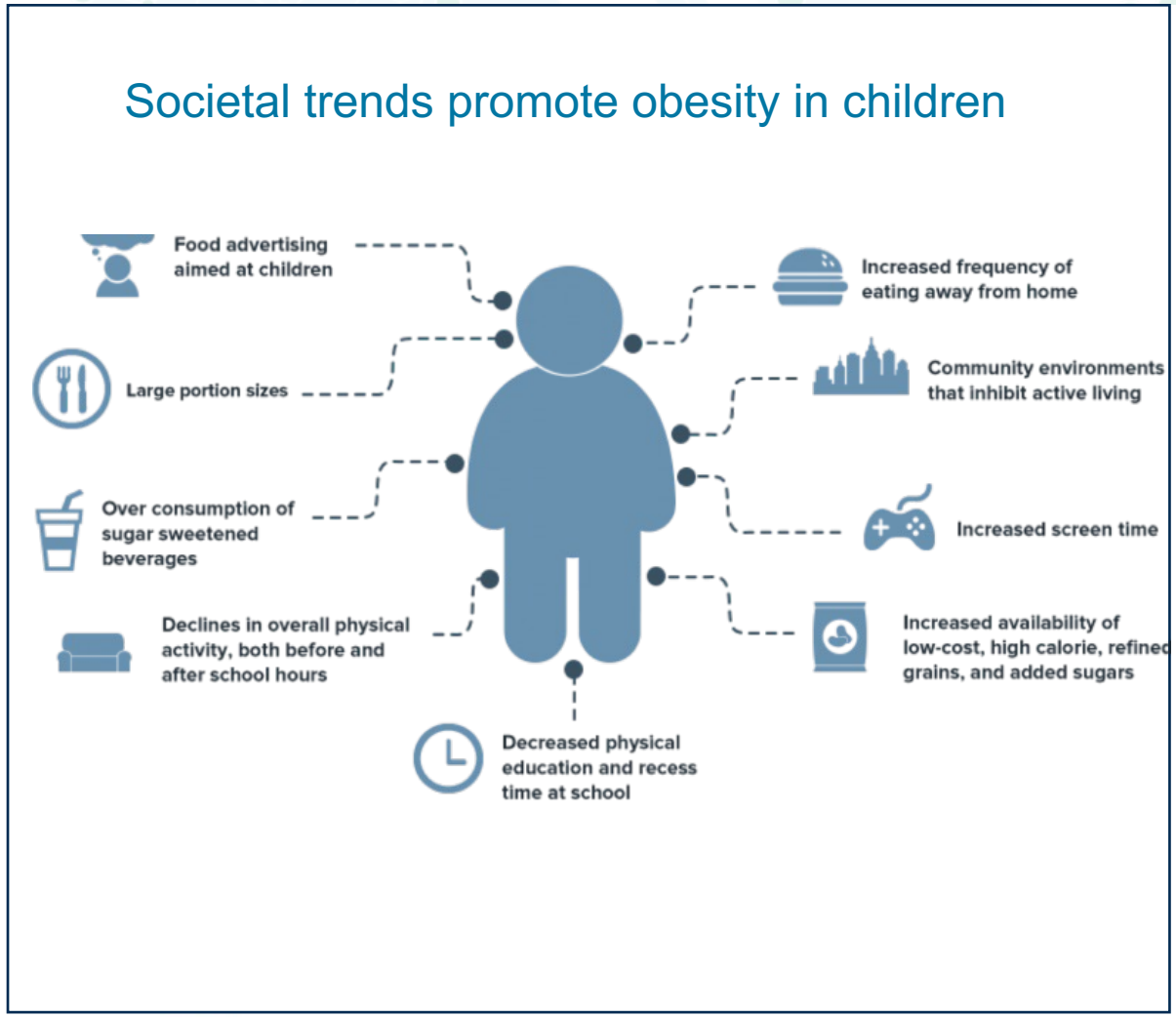
WHO estimates, 2023

Lancet. 2024 Mar 16;403(10431):1027-1050.

DISPROPORTIONALLY AFFECTING THE SOCIOECONOMIC DISADVANTAGED

Obesogenic environment of low income and food insecurity

DISPROPORTIONALLY AFFECTING THE FUTURE GENERATIONS



Thinness
Obesity

High-income English-speaking countries
Northwestern Europe
Southwestern Europe
Central Europe

Eastern Europe
Southern Latin America
Central Latin America
Andean Latin America

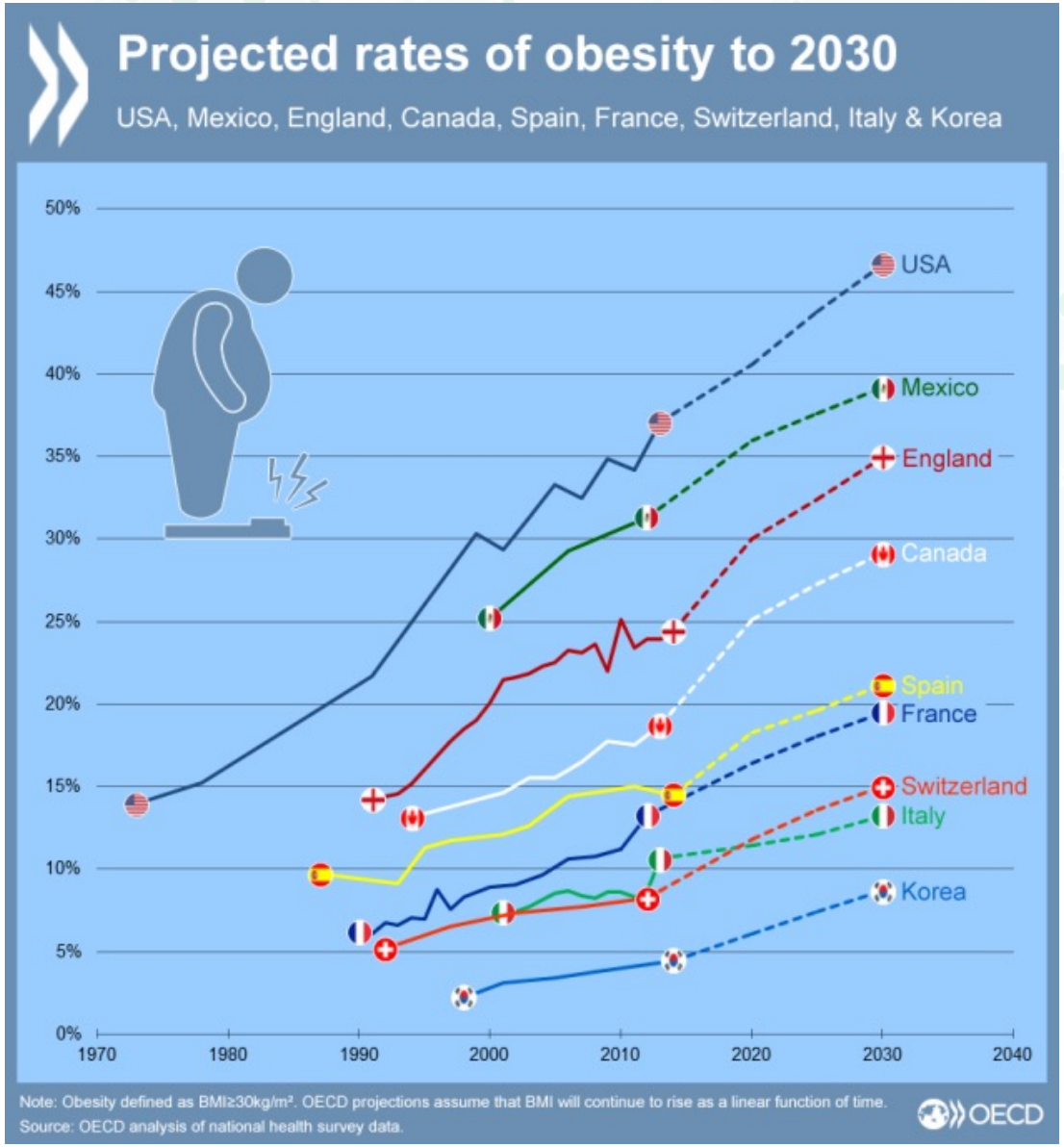
The Caribbean
East Asia and the Pacific
Southeast Asia
South Asia

Central Asia
Middle East and north Africa
Polynesia and Micronesia
Melanesia

East Africa
West Africa
Central and southern Africa
Other sub-Saharan Africa

Lancet. 2024 16;403(10431):1027-1050.

PROJECTIONS IN ADULTS



Pesimistic projections in adults assuming to rise as a linear function of time

24% of the global population will have obesity by 2035

Table 1.1: Global overweight and obesity 2020–2035

Numbers of people (aged over 5 years) and percentage of the population with overweight or obesity*

	2020	2025	2030	2035
Number with overweight or obesity (BMI≥25kg/m²) (millions)	2,603	3,041	3,507	4,005
Number with obesity (BMI ≥30kg/m²) (millions)	988	1,249	1,556	1,914
Proportion of the population with overweight or obesity (BMI ≥25kg/m²)	38%	42%	46%	51%
Proportion of the population with obesity (BMI ≥30kg/m²)	14%	17%	20%	24%

** For children and adolescents, overweight and obesity are defined using the WHO classification of +1SD and +2SD above median growth reference.*

World Obesity Federation, World Obesity Atlas 2023.
https://data.worldobesity.org/publications/?cat=19

PROJECTIONS IN CHILDREN

The NEW ENGLAND JOURNAL of MEDICINE

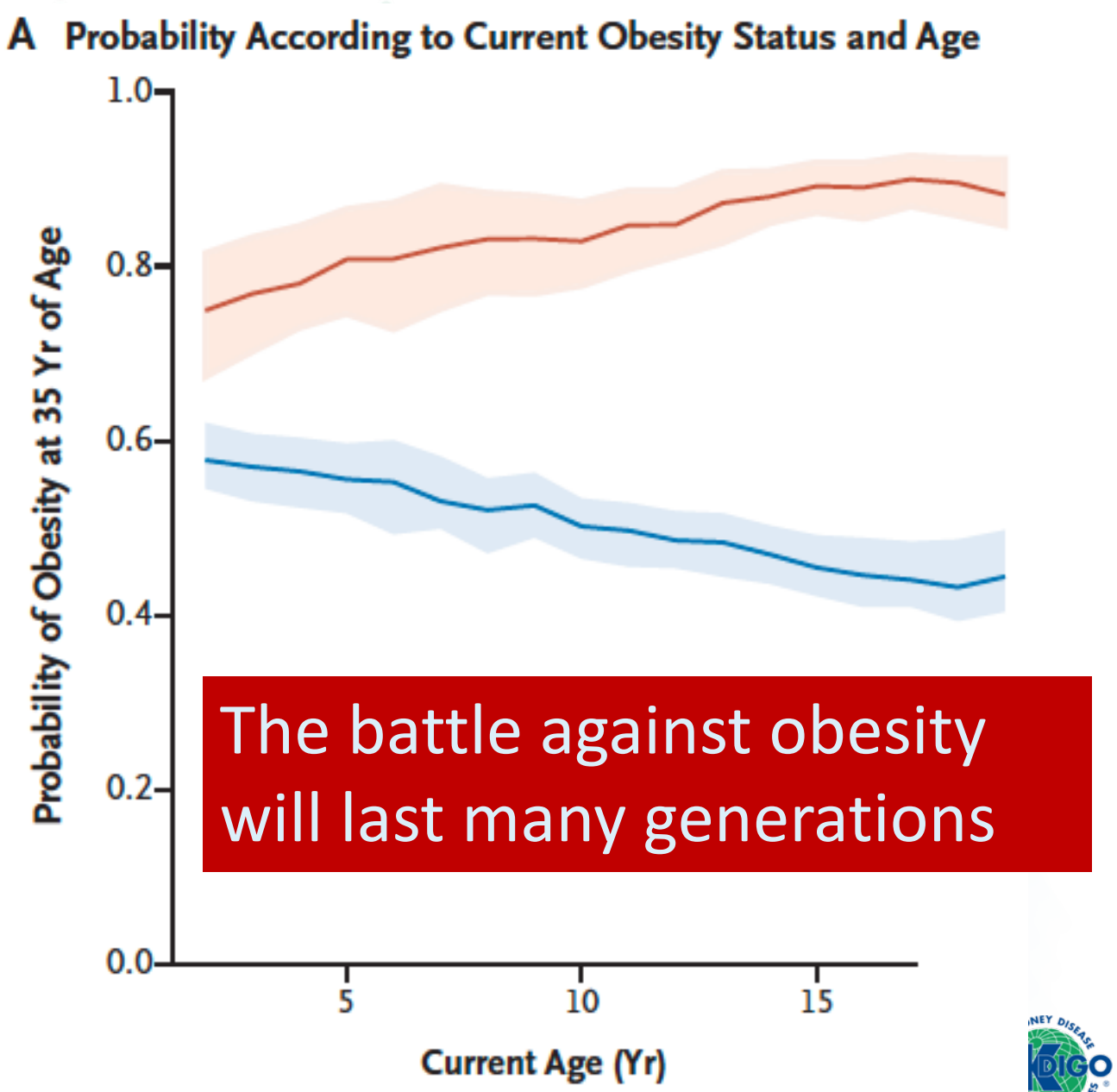
ORIGINAL ARTICLE

Simulation of Growth Trajectories of Childhood Obesity into Adulthood

Zachary J. Ward, M.P.H., Michael W. Long, Sc.D., Stephen C. Resch, Ph.D., Catherine M. Giles, M.P.H., Angie L. Cradock, Sc.D., and Steven L. Gortmaker, Ph.D.

- 50-60% of todays non-obese children will become obese by age 35
- 75%-90% of todays obese children will remain obese by age 35.

The potential for reducing obesity prevalence in adults might be largely determined by leaner children entering adulthood, rather than reducing prevalence in the current generations of adults.



The battle against obesity will last many generations

NEJM. 2017 Nov 30;377(22):2145-2153.

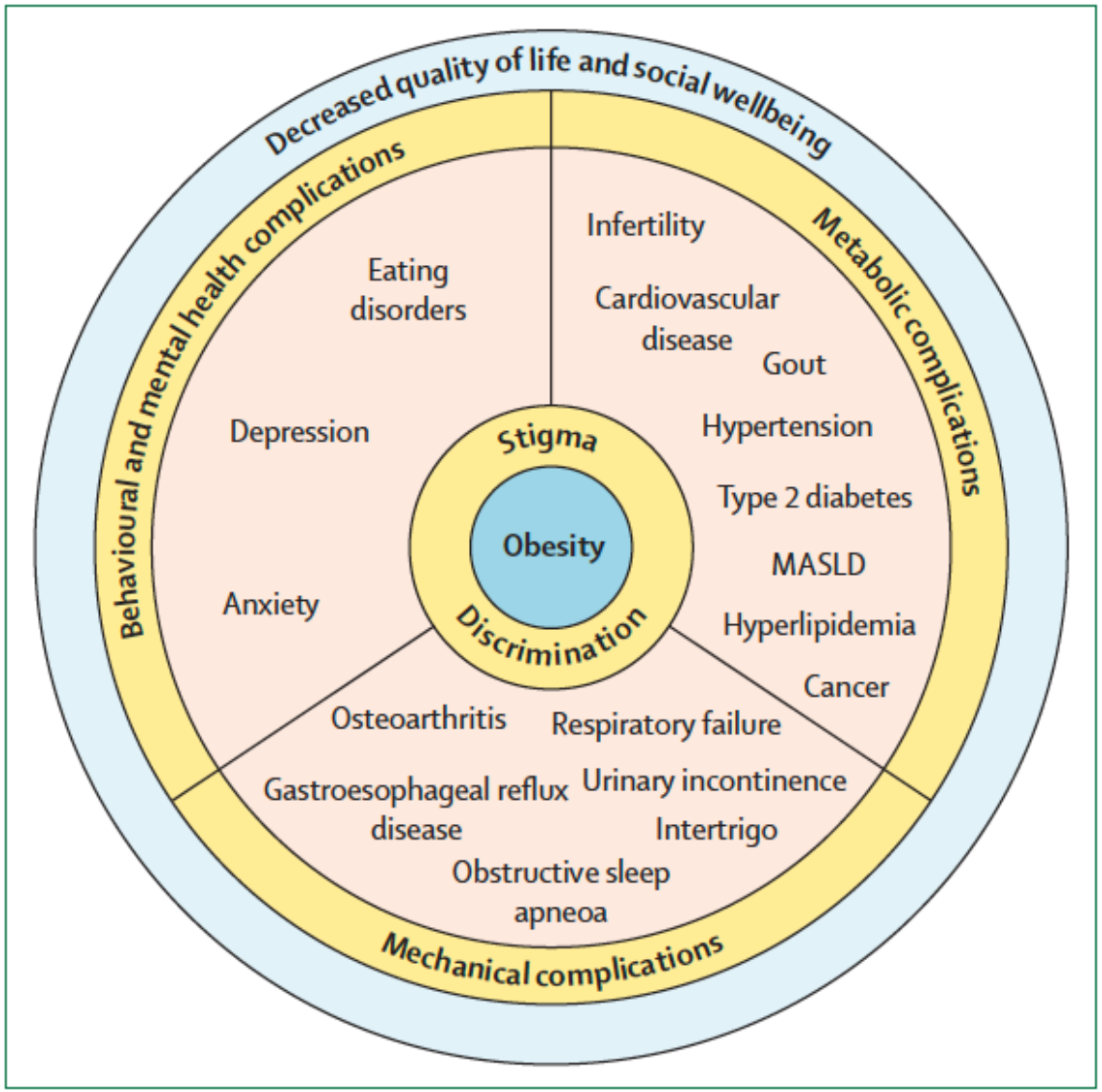


Figure 1: The wide-ranging complications of obesity

Lancet. 2024 Aug 16:S0140-6736(24)01210-8.

HEALTH CONSEQUENCES OF OBESITY

In general-medicine reviews, CKD is seldom recognized as a consequence of obesity.

- Not recognized by WHO or Center for Diseases Control (CDS) in the US
- Described as a consequence of other obesity-related complications: diabetes, hypertension and CVD

POSTULATED MECHANISMS OF OBESITY LEADING TO CKD

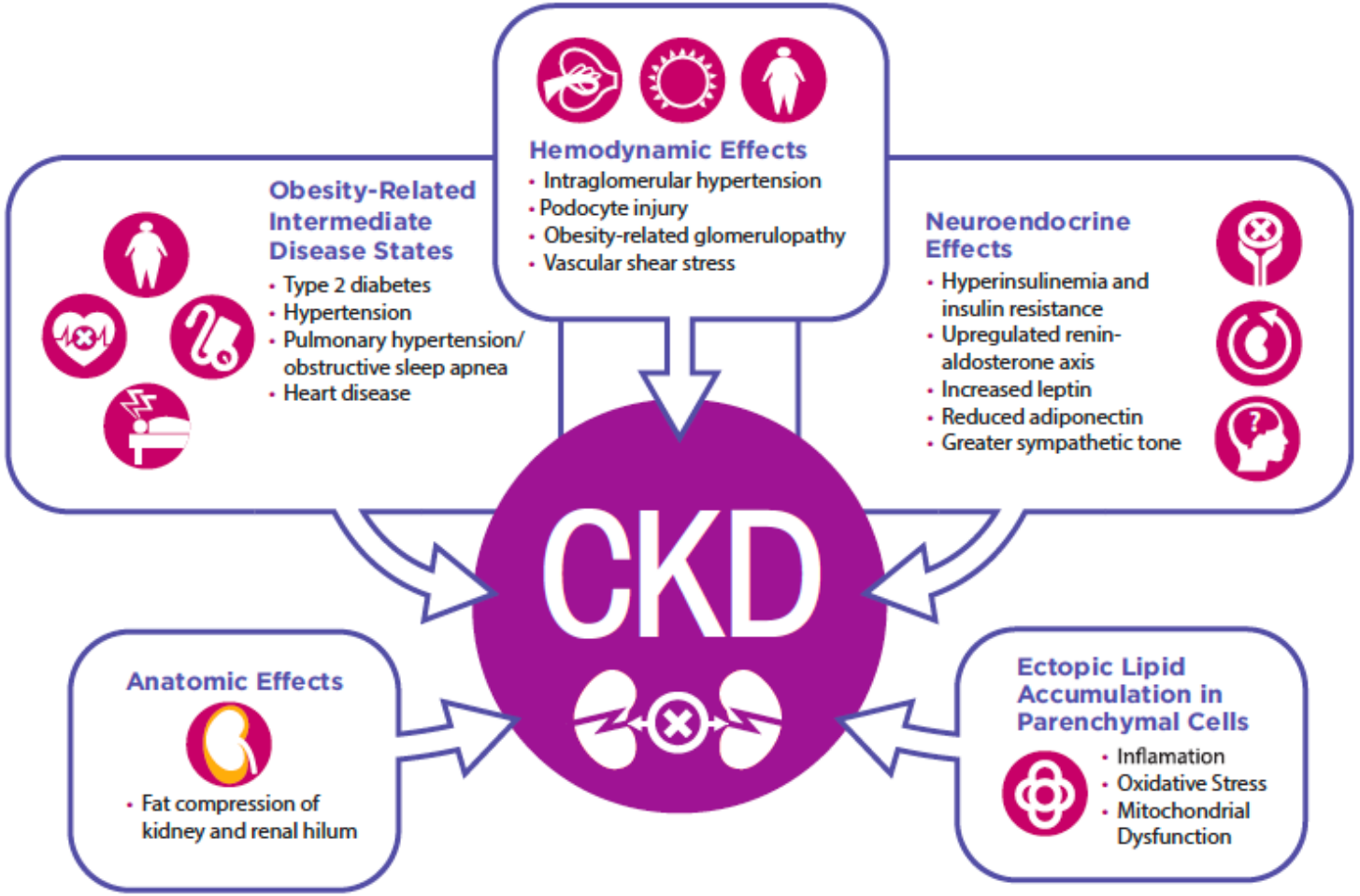


Figure 1. Mechanisms through which obesity leads to kidney damage. Abbreviation: CKD, chronic kidney disease.

In histopathological examination often found:

- glomerular hyperfiltration
- glomerular hypertrophy
- increased glomerular capillary radius
- decreased podocyte density

Am J Kidney Dis. 2022 Dec;80(6):783-793.

OPEN ACCESS

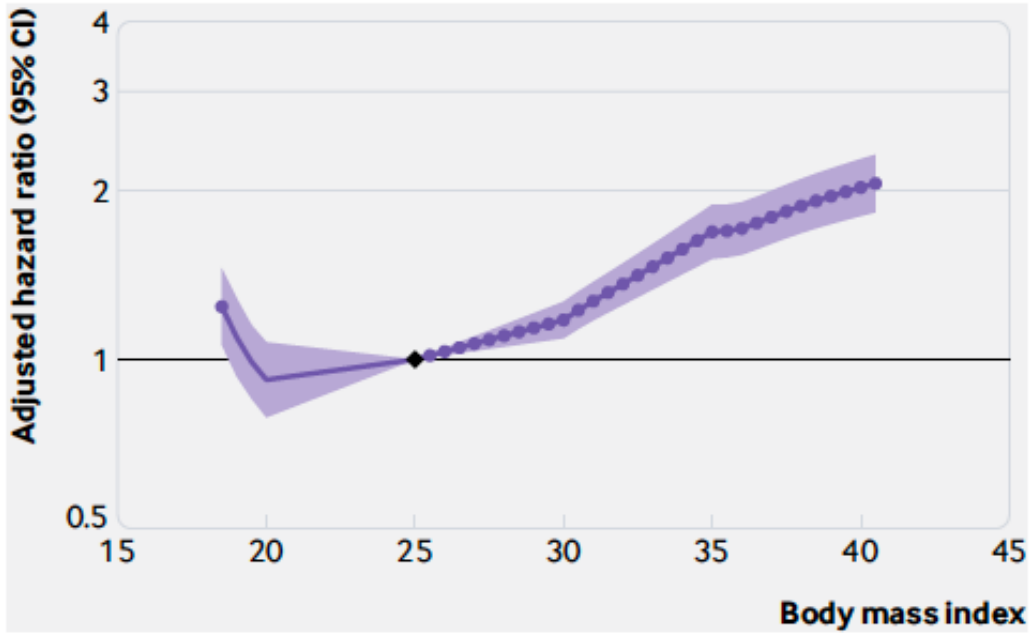
Check for updates

Adiposity and risk of decline in glomerular filtration rate: meta-analysis of individual participant data in a global consortium

Alex R Chang,[1] Morgan E Grams,[2] Shoshana H Ballew,[2] Henk Bilo,[3] Adolfo Correa,[4] Marie Evans,[5] Orlando M Gutierrez,[6,7] Farhad Hosseinpanah,[8] Kunitoshi Iseki,[9,10] Timothy Kenealy,[11] Barbara Klein,[12] Florian Kronenberg,[13] Brian J Lee,[14] Yuanying Li,[15] Katsuyuki Miura,[16] Sankar D Navaneethan,[17] Paul J Roderick,[18] Jose M Valdivielso,[19] Frank L J Visseren,[20] Luxia Zhang,[21] Ron T Gansevoort,[22] Stein I Hallan,[23,24] Andrew S Levey,[25] Kunihiro Matsushita,[2] Varda Shalev,[26] Mark Woodward,[2,27,28] On behalf of the CKD Prognosis Consortium (CKD-PC)

39 general population cohorts (n=5 459 014)

GFR decline: eGFR decline ≥40%, KRT or eGFR <10 mL/min/1.73 m_2



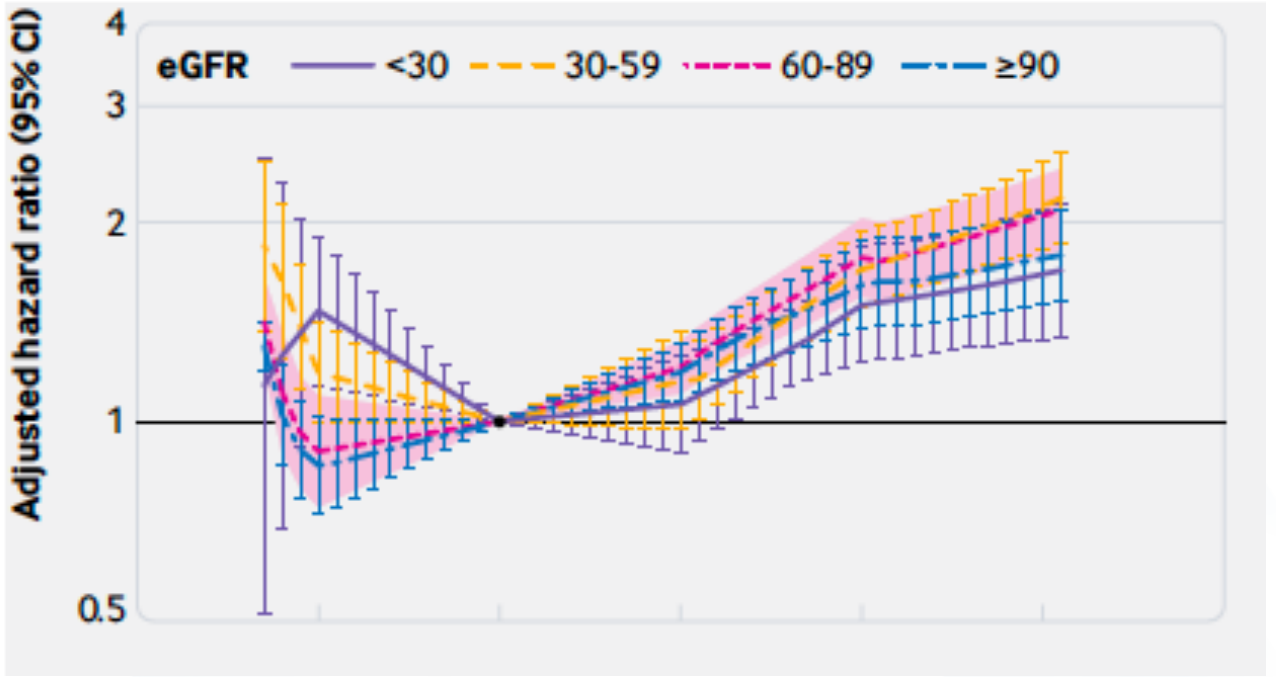


Fig 1 | Association between body mass index and risk of decline in glomerular filtration rate in general population cohorts, as shown by meta-analysed hazard ratios and 95% confidence intervals related to body mass index. Association is modelled by linear splines with knots at body mass indices 20, 25, 30, and 35. Circles indicate points with significant differences in risk from the reference point at body mass index 25

BMJ 2019;364:k5301 http://dx.doi.org/10.1136/bmj.k5301

Research

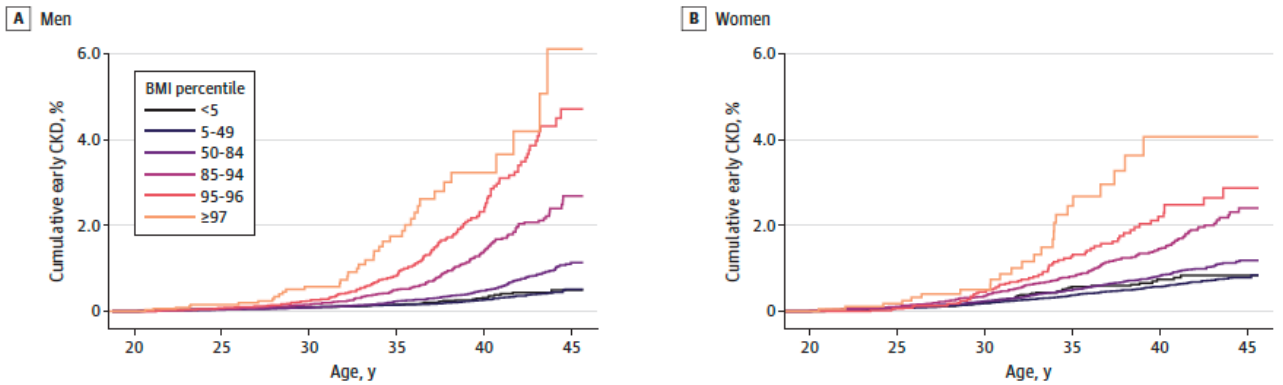
JAMA Pediatrics | Original Investigation

Adolescent Body Mass Index and Early Chronic Kidney Disease in Young Adulthood

Avishai M. Tsur, MD, MHA; Inbal Akavian, MD; Regev Landau, MD; Estela Derazne, MSc; Dorit Tzur, MBA; Asaf Vivante, MD, PhD; Ehud Grossman, MD; Ran S. Rotem, PhD; Boris Fishman, MD, MPH; Orit Pinhas-Hamiel, MD; Arnon Afek, MD, MHA; Josef Coresh, MD, PhD; Gabriel Chodick, PhD; Gilad Twig, MD, PhD

600.000 adolescents aged 16-20 years attending health examinations in Israel.
Outcome: CKD stages 1-2 (early CKD)

Figure 2. Incidence of Early Chronic Kidney Disease (CKD) by Adolescent Body Mass Index (BMI) Status

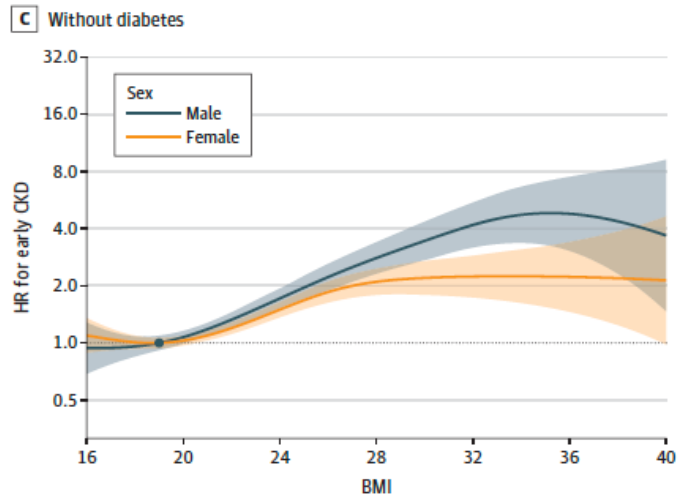


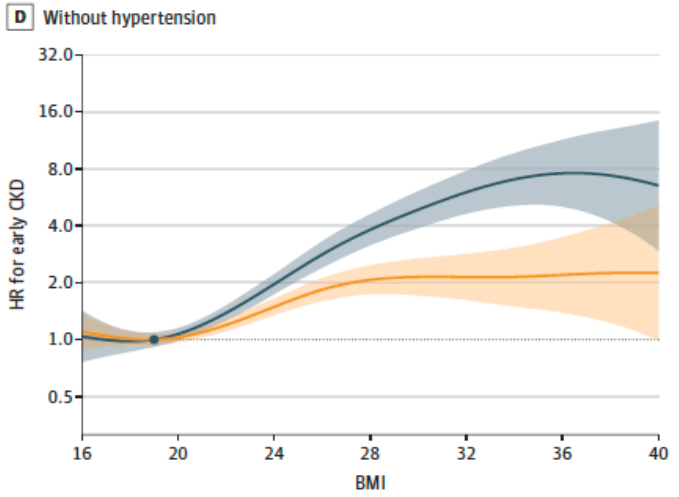
No. at risk by BMI percentile

<5	16537	17762	14437	9758	4872	635
5-49	101676	106344	84666	55649	28625	3579
50-84	82173	79218	59607	37355	18986	2359
85-94	26749	23420	16420	9786	4549	531
95-96	14640	11922	7769	4475	1886	222
≥97	3726	2650	1508	787	267	25

No. at risk by BMI percentile

<5	9157	9244	7261	4732	2436	319
5-49	88180	89094	70076	46108	24003	2992
50-84	77651	74916	57079	37418	19796	2394
85-94	21943	19338	13968	8998	4545	546
95-96	6707	5471	3734	2233	1096	116
≥97	2002	1430	856	450	188	19





Early signs of albuminuria more likely to occur in adolescents with obesity, often appearing before the age of 30 years, and regardless of the presence of DM or HT

JAMA Pediatr. 2024 Feb 1;178(2):142-150.

REGARDLESS OF METABOLIC HEALTH OR GENETIC CONFOUNDING

Annals of Internal Medicine ORIGINAL RESEARCH

Metabolically Healthy Obesity and Development of Chronic Kidney Disease

A Cohort Study

Yoosoo Chang, MD, PhD; Seungho Ryu, MD, PhD; Yuni Choi, BS; Yiyi Zhang, PhD; Juhee Cho, PhD; Min-Jung Kwon, MD, PhD; Young Youl Hyun, MD, PhD; Kyu-Beck Lee, MD, PhD; Hyang Kim, MD, PhD; Hyun-Suk Jung, MD; Kyung Eun Yun, MD, PhD; Jiin Ahn, MSPH; Sanjay Rampal, MD, PhD; Di Zhao, PhD; Byung-Seong Suh, MD, PhD; Eun Cheol Chung, MD, PhD; Hocheol Shin, MD, PhD; Roberto Pastor-Barriuso, PhD; and Eliseo Guallar, MD, DrPH

Metabolic health defined as:

- No prediabetes, diabetes, or using blood glucose–lowering agents
- No prehypertension, hypertension, or using of blood pressure–lowering agents
- No hypertriglyceridemia or using lipid-lowering agents
- No insulin resistance
- High HDL cholesterol levels

Ann Intern Med. 2016 Nov 15;165(10):744-745.

www.kidney-international.org clinical investigation

Higher body mass index is associated with incident diabetes and chronic kidney disease independent of genetic confounding

Check for updates

Hong Xu[1,2], Ralf Kuja-Halkola[1], Xu Chen[1], Patrik K.E. Magnusson[1], Per Svensson[3,4,5] and Juan-Jesus Carrero[1,5]

29,136 Swedish twins with no history of CKD or diabetes

Heavier twins had higher incidence rates of both CKD and diabetes than their leaner siblings, particularly when BMI differed by >2 kg/m2

Kidney Int. 2019 May;95(5):1225-1233.

- **Q:** Isn't there sufficient evidence to propose routine screening for CKD in people with obesity?

FAR TOO MANY PEOPLE WITH CKD STAGES 3-5ND LIVE WITH OBESITY

- 72% with elevated waist circumference
- 50% with obesity (BMI ≥30)
- 26% with severe obesity (BMI ≥35)

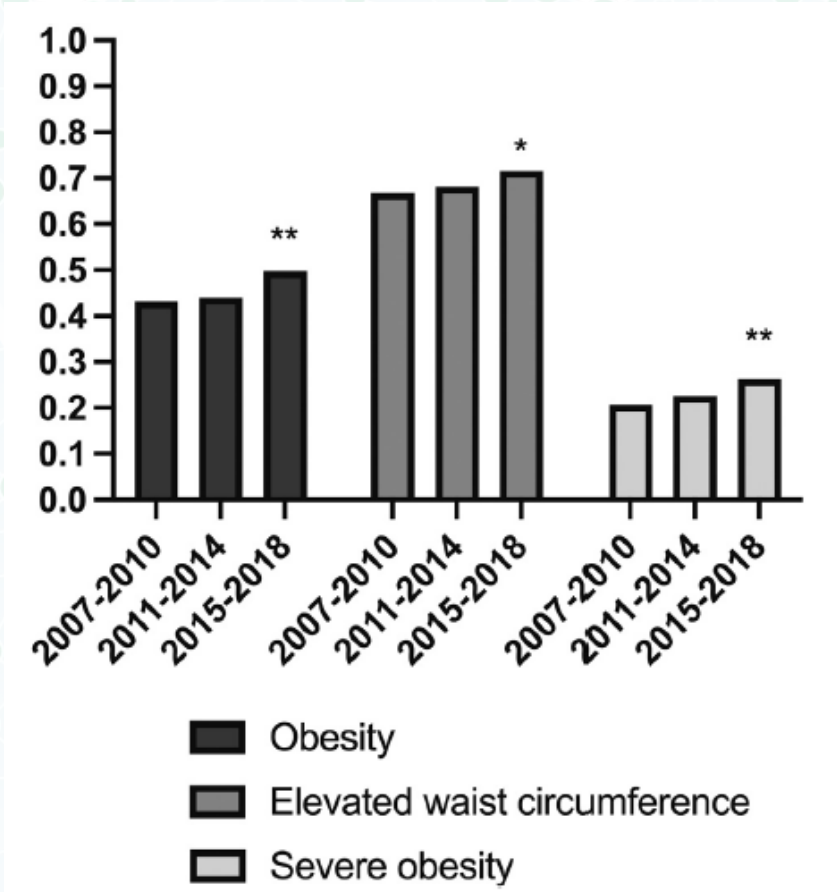


Figure 1. Prevalence of obesity, abdominal obesity, and severe obesity in chronic kidney disease. Prevalence of obesity (BMI ≥ 30 kg/m^2), elevated waist circumference (>102 cm for men, >88 cm for women), and severe obesity (BMI ≥ 35 kg/m^2) in patients with chronic kidney disease. Data from NHANES 2007-2018. Abbreviation: BMI, body mass index. *P = 0.02 for linear trend. **P < 0.01 for linear trend.

Am J Kidney Dis. 2023 Dec;82(6):762-771.

PROGRESSION TO ESKD IS FASTER IN PEOPLE WITH CKD AND OBESITY

CLINICAL EPIDEMIOLOGY www.jasn.org

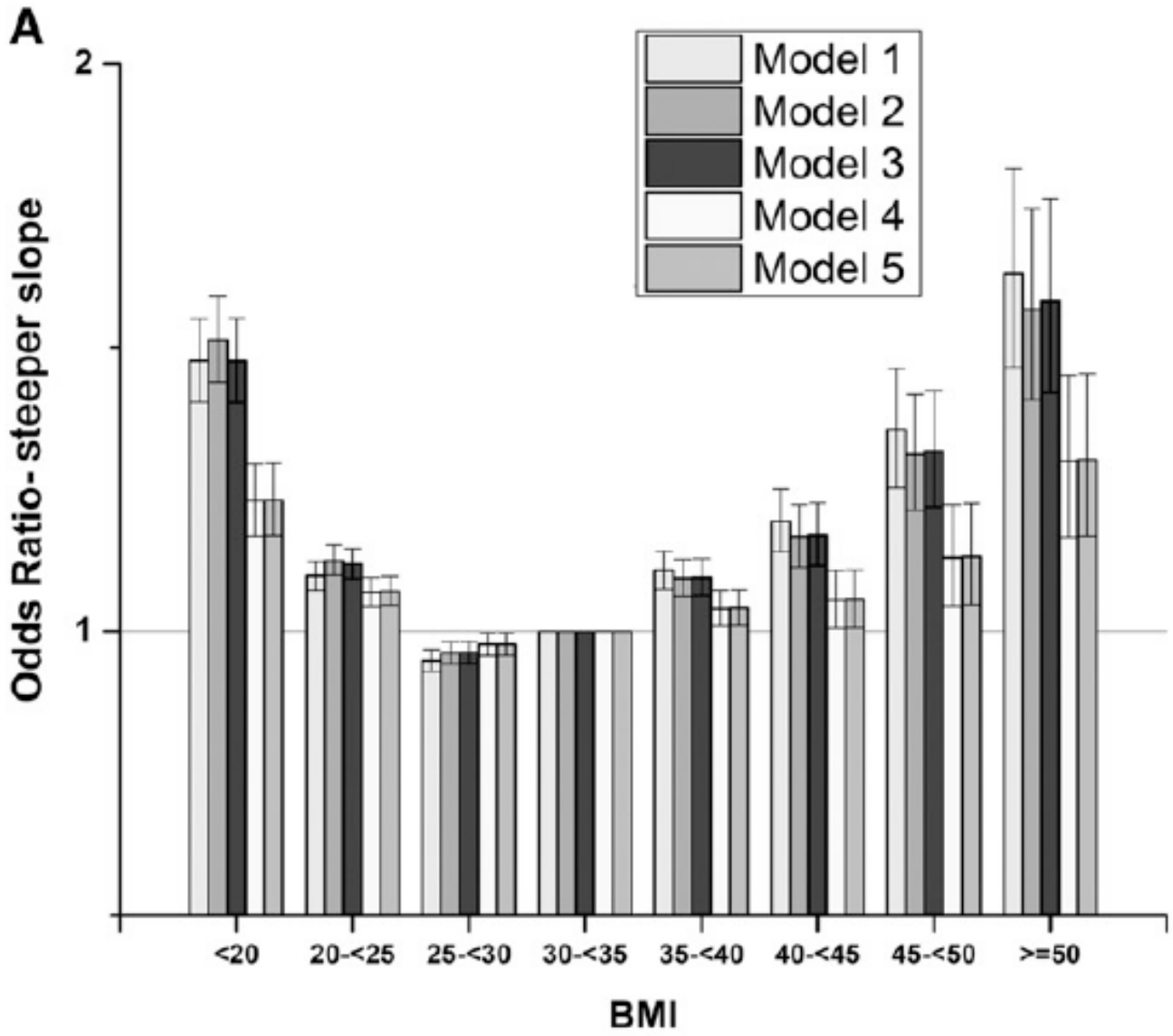
Association of Body Mass Index with Outcomes in Patients with CKD

Jun Ling Lu,* Kamyar Kalantar-Zadeh,† Jennie Z. Ma,‡ L. Darryl Quarles,* and Csaba P. Kovesdy*§

Almost 0.5 Million US veterans with CKD
Outcome: ESKD

Higher BMI categories linked to a more rapid progression to ESKD

Also lower BMI categories



J Am Soc Nephrol. 2014 Sep;25(9):2088-96.

OBESITY PREVAILS IN DIALYSIS POPULATIONS

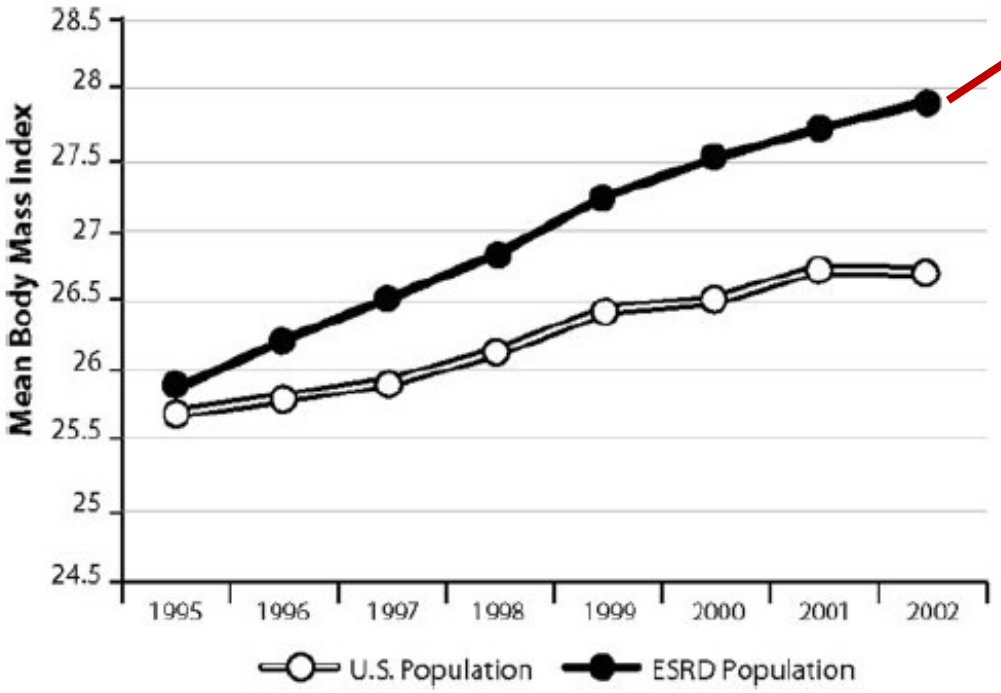


Figure 1. Temporal trends in mean body mass index (kg/m^2) among the incident adult ESRD patient population by year of first permanent dialysis initiation and in the total adult US population (Behavioral Risk Factor Surveillance System) for the corresponding year. Data are age adjusted for the 2000 US census.

Kramer H. J Am Soc Nephrol. 2006 May;17(5):1453-9.

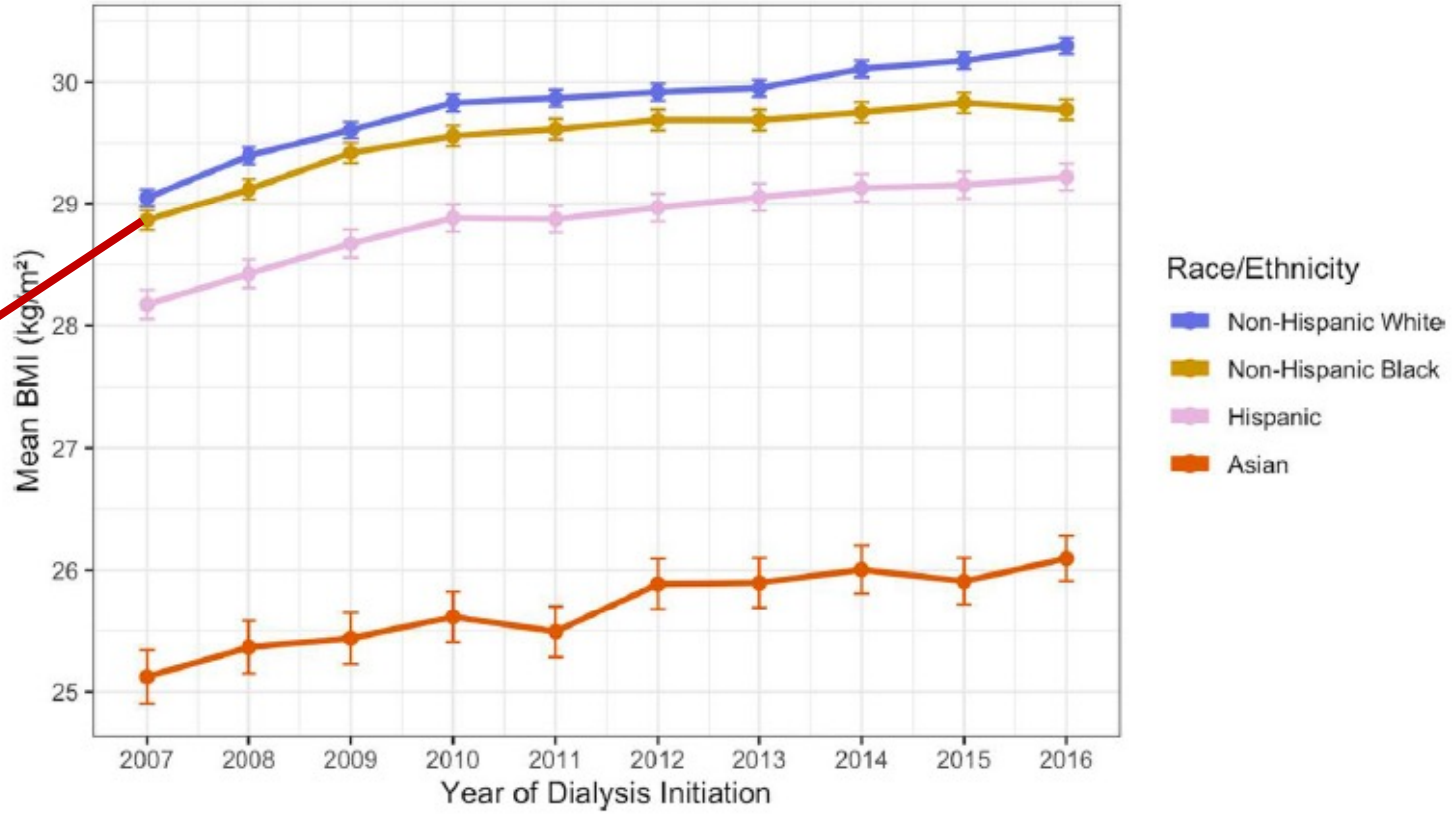
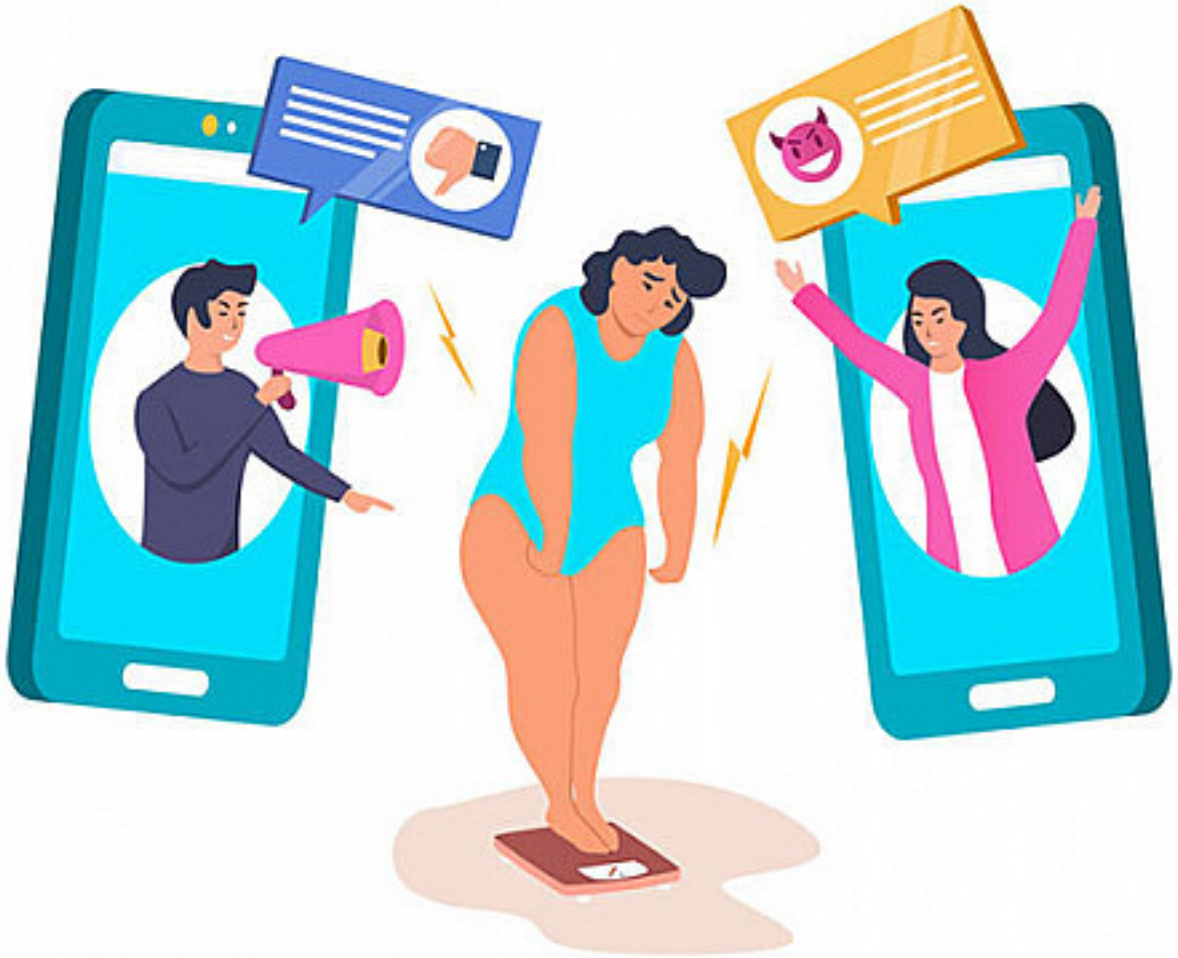


FIGURE 1. BMI trends of adult incident dialysis patients in the United States by race/ethnicity group (2007–2016). Figure depicts age- and sex-adjusted mean BMI with 95% confidence intervals by race/ethnicity. The 4 most prevalent racial/ethnic subgroups are shown in blue (non-Hispanic White), yellow (non-Hispanic Black), pink (Hispanic), and orange (Asian). BMI, body mass index.

Transplantation. 2022 Nov 1;106(11):e488-e498.

PEOPLE WITH CKD AND OBESITY FACE MANY CHALLENGES

EMOTIONAL CHALLENGES: WEIGHT STIGMA



Social rejection and devaluation based on a person's body weight.

Associated with low self-steem, depression, mental health problems, suicide attempts

Sometimes coping with this stigma by alcohol and substance use, overeating to deal with negative emotions, and avoiding health care settings or social encounters

Weight stigma also present in healthcare providers: assuming overeating behaviour, low compliance, laziness or unwillingness to engage in lifestyle advice. This bias results in reduced quality of care

BMC Med. 2018 Aug 15;16(1):123.

Plos One. 2012;7(11):e48448.

OBESITY HINDERS KIDNEY FUNCTION ASSESSMENT AND MONITORING

Clearance marker accuracy impaired in obesity

1. Creatinine influenced by muscle mass (higher in obesity)
2. Cys C affected by adiposity

- **Q:** How to best estimate kidney function in obesity?
- **Q:** How to best estimate kidney function after large weight losses (e.g. bariatric surgery, pharmacological treatments)?

Wi **tion?**

- hat combine both creatinine and cystatin C?
- delines suggest de-indexation at BMI extremes
- Done outside nephrologist care?
  - Do incorrect estimates alter risk/benefit of treatments?

UACR and UPCR often underestimate proteinuria in obesity (the denominator creatinuria increases)

- Underdiagnosis, delayed treatments
- Better use 24-h collections rather than spot determinations?

OBESITY HINDERS THE MANAGEMENT OF CKD

Difficulties in **placement of a permanent access** J Am Coll Surg. 2015 Dec;221(6):1067-72.

Physical challenges that may affect the **diagnostic performance of medical devices**: electrocardiograms, echocardiography, magnetic resonance and tomography

J Am Coll Cardiol. 2023 Feb 7;81(5):490-504.

Changes in **pharmacodynamics/pharmacokinetics**

- Increased volume of distribution (not only lipophilic drugs)
- Increased renal clearance by higher cardiac output
- Increased hepatic metabolism

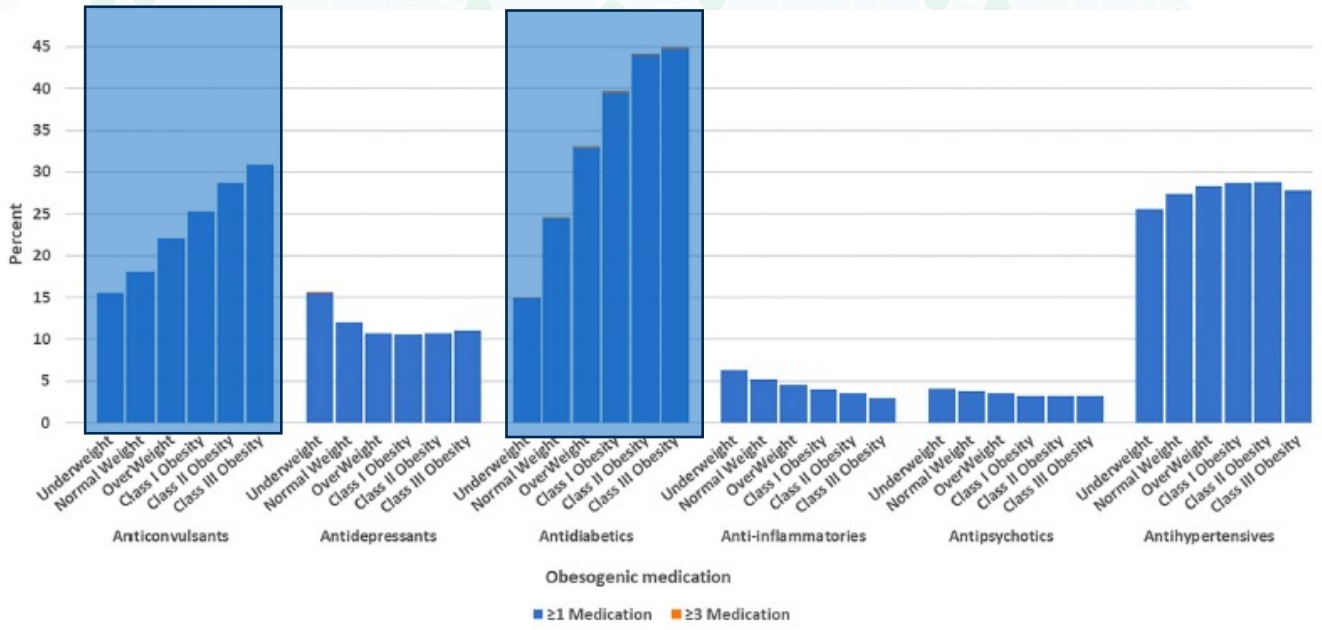
    - Considerations for antiplatelet choice because of high on-treatment platelet reactivity
    - Considerations for anticoagulant dose to balance risks of thromboembolism vs bleeding.

Increased prevalence of comorbid conditions (multimorbidity) that require many medications for its management (polypharmacy)

Obesogenic medications
Common drugs promote weight gain

Antidepressants (3-4 lbs)	Amitriptyline	Nortriptyline	Paroxetine
	Citalopram	Sertraline	
Anticonvulsants (~2-5 lbs)	Pregabalin	Carbamazepine	
	Gabapentin	Valproic Acid	
Antidiabetics (5-13 lbs)	Glipizide	Glyburide	
	Insulins	Pioglitazone	
Antipsychotics (2-34 lbs)	Olanzapine	Clozapine	
	Quetiapine	Perphenazine	
Antihypertensives (2-8 lbs)	Atenolol	Propranolol	
	Metoprolol		
Opioids (Sparse data)	Hydrocodone		
	Oxycodone		
Antihistamines & Steroids (Up to 11 lbs for steroids)	Diphenhydramine		
	Prednisone		

ESKD patients with obesity more likely to consume obesogenic medications



Access to listing[a]	Obesogenic medication	
	No	Yes
Overall	Reference	0.94 (0.92–0.96)
Underweight[c]	Reference	0.94 (0.82–1.07)
Normal weight[c]	Reference	0.93 (0.90–0.97)
Overweight[c]	Reference	0.95 (0.92–0.98)
Class I obesity[c]	Reference	0.90 (0.87–0.93)
Class II obesity[c]	Reference	0.92 (0.87–0.97)
Class III obesity[c]	Reference	0.80 (0.74–0.86)
		$p < 0.001$[d]

Reducing the likelihood of being on KT listing

Clin Transplant. 2024 Aug;38(8):e15414.

OBESITY IMPEDES ACCESS TO KIDNEY TRANSPLANTATION

Irrespective of BMI, patient survival is improved if transplanted (vs staying on dialysis).

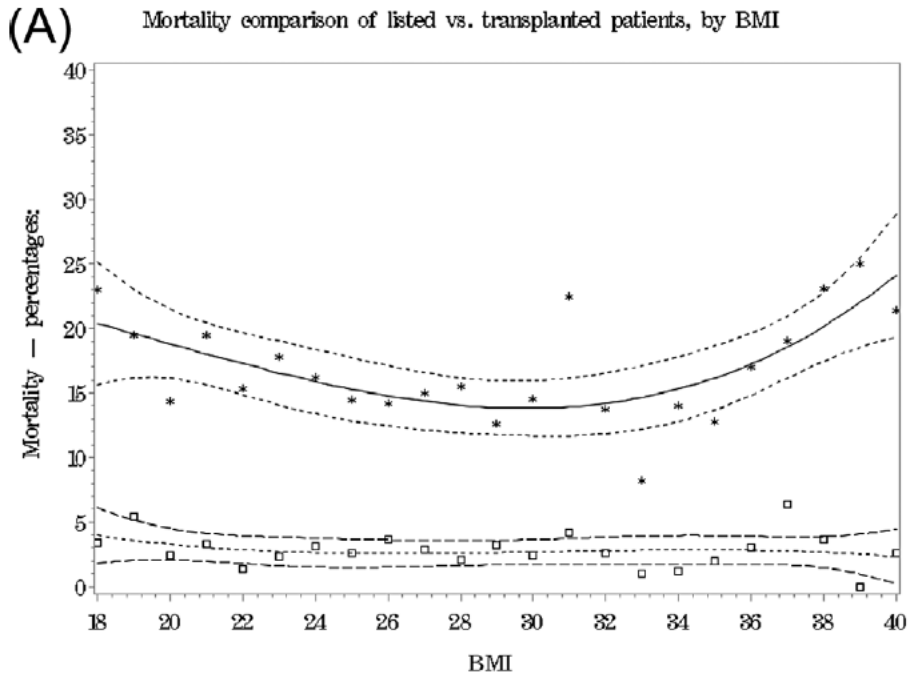
Nephrol Dial Transplant (2015) 30: 1403–1411
doi: 10.1093/ndt/gfv214
Advance Access publication 4 June 2015

ndt Nephrology Dialysis Transplantation

Original Article

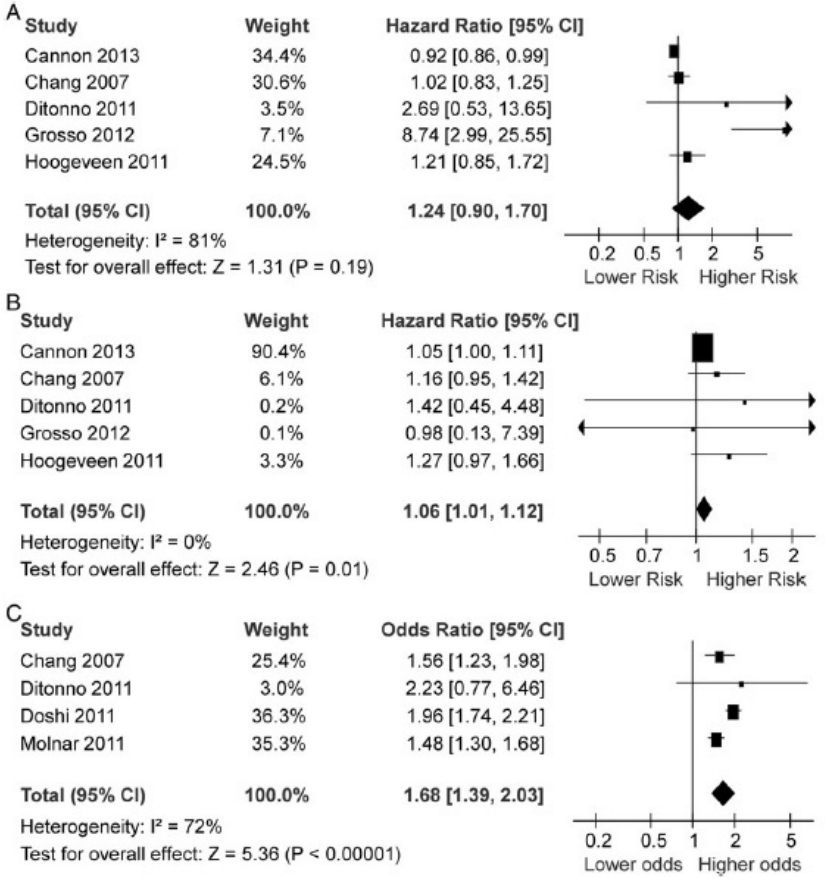
Recipient obesity and outcomes after kidney transplantation: a systematic review and meta-analysis

Christopher J. Hill[1], Aisling E. Courtney[1], Christopher R. Cardwell[2], Alexander P. Maxwell[1], Giuseppe Lucarelli[3], Massimiliano Veroux[4], Frederico Furriel[5], Robert M. Cannon[6], Ellen K. Hoogeveen[7], Mona Doshi[8] and Jennifer A. McCaughan[1]



17681 UK patients in the waiting list 2004-2010

Am J Transplant. 2015 Sep;15(9):2378-86.



Higher likelihood of delayed graft failure,

But only a small increased risk of graft loss

Similar survival

Compared to recipients with normal BMI.

Q: Still, many hospitals globally require BMI<30 kg/m^2 to be enrolled in the Tx waiting list (larger thresholds in some countries).

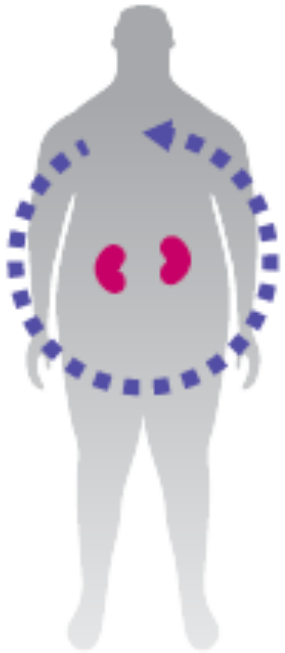
- Time to reconsider?

Difficulties during surgery. Robotic surgery? Pre-Tx bariatric surgery?

Obesity may pose challenges **<u>to any Tx management (not only kidney Tx)</u>**:

- Obesity-related complications (type 2 diabetes, hypertension, and cardiovascular disease)
- Hyperfiltration
- Inflammation induced by excess adipose tissue
- Increased risk of perioperative complications.
- Changes in bioavailability of immunosuppressive agents = risks of immunologic injury to the allograft.

BROAD ARRAY OF HEALTH CHALLENGES WITH OBESITY

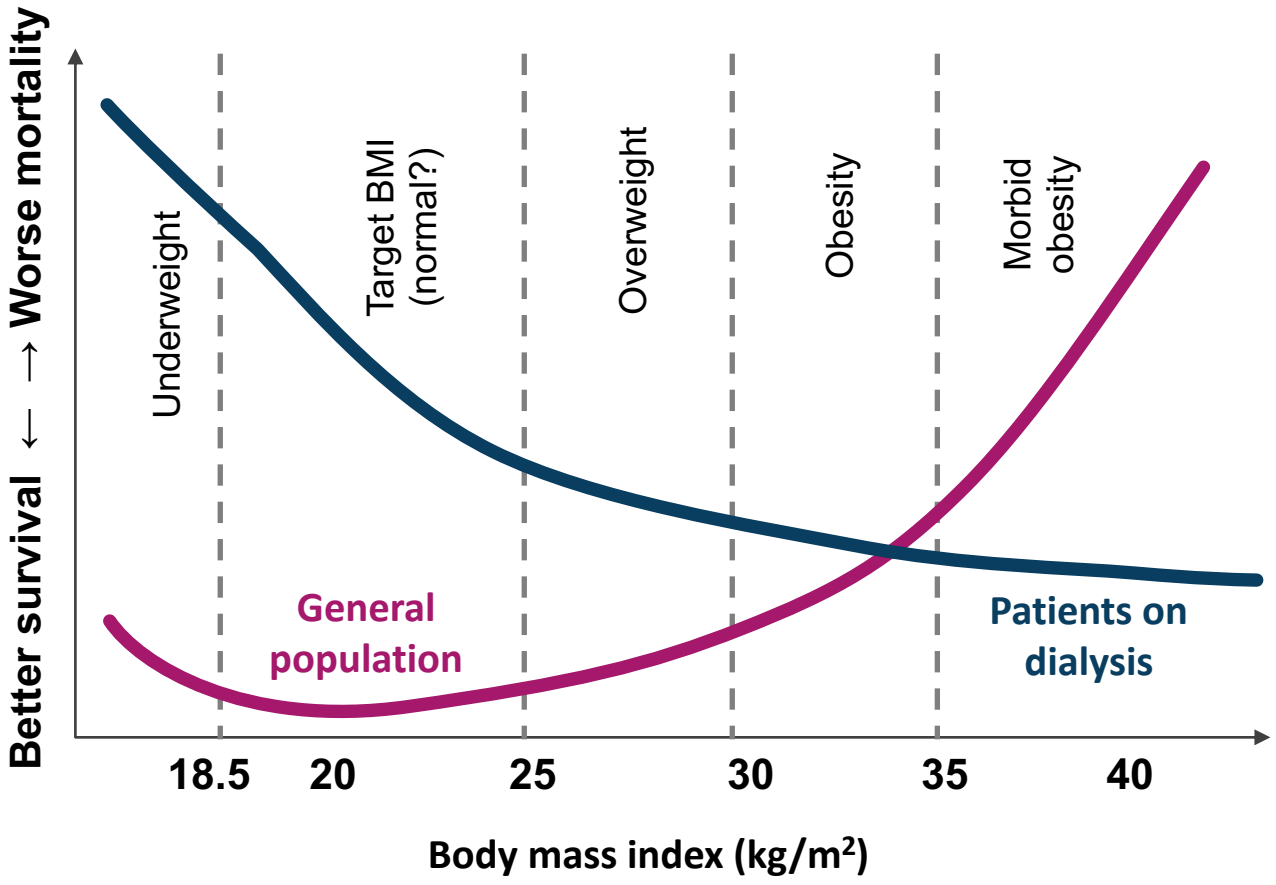


Complications of Obesity	Stages of CKD							
	No CKD	1	2	3	4	5	5D	5T
Increased Risk of Developing CKD	●							●
Increased Risk of CKD Progression		●	●	●	●	●		●
Decreased Access to Kidney Transplantation						●	●	●
Increased Risk of Cardiovascular Disease	●	●	●	●	●	●	●	●
Increased Hospitalizations	●	●	●	●	●	●	●	●
Increased Healthcare Costs	●	●	●	●	●	●	●	●
Decreased Quality of Life	●	●	●	●	●	●	●	●
Decreased Life Expectancy	●	●	●	●	●	●	*	●

Am J Kidney Dis. 2022 Dec;80(6):783-793.

THE OBESITY PARADOX OF PATIENTS ON DIALYSIS

(reverse epidemiology– effect modification – risk factor paradox)



Kalantar-Zadeh K, et al. *Kidney Int Rep*. 2017;2(2):271-281.

BMI HAS MANY LIMITATIONS AS A CLINICAL DECISION TOOL

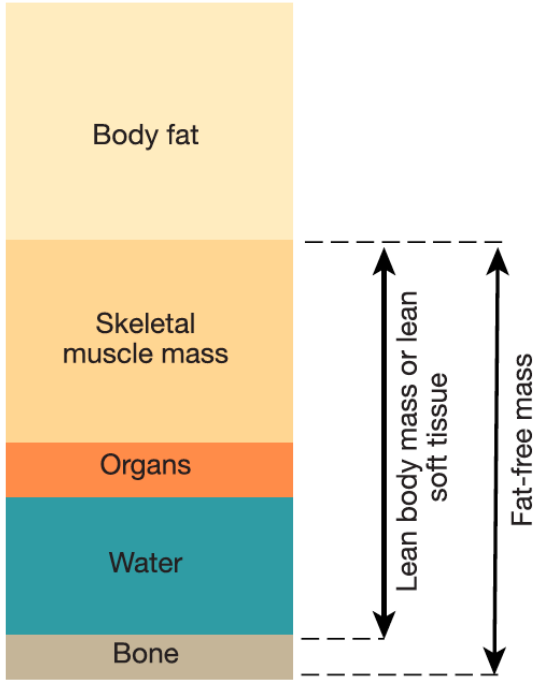


Figure 1 | Body composition compartments; differences in the estimation of fat-free mass and lean soft-tissue/lean body mass. Residual mass considers connective tissue and blood.

Kidney Int. 2016 Jul;90(1):53-66.

Semin Dial. 2015 Jan-Feb;28(1):48-58.

1. BMI does not differentiate **fat from muscle**

2. BMI does not capture the a**ging-changes** in body composition.

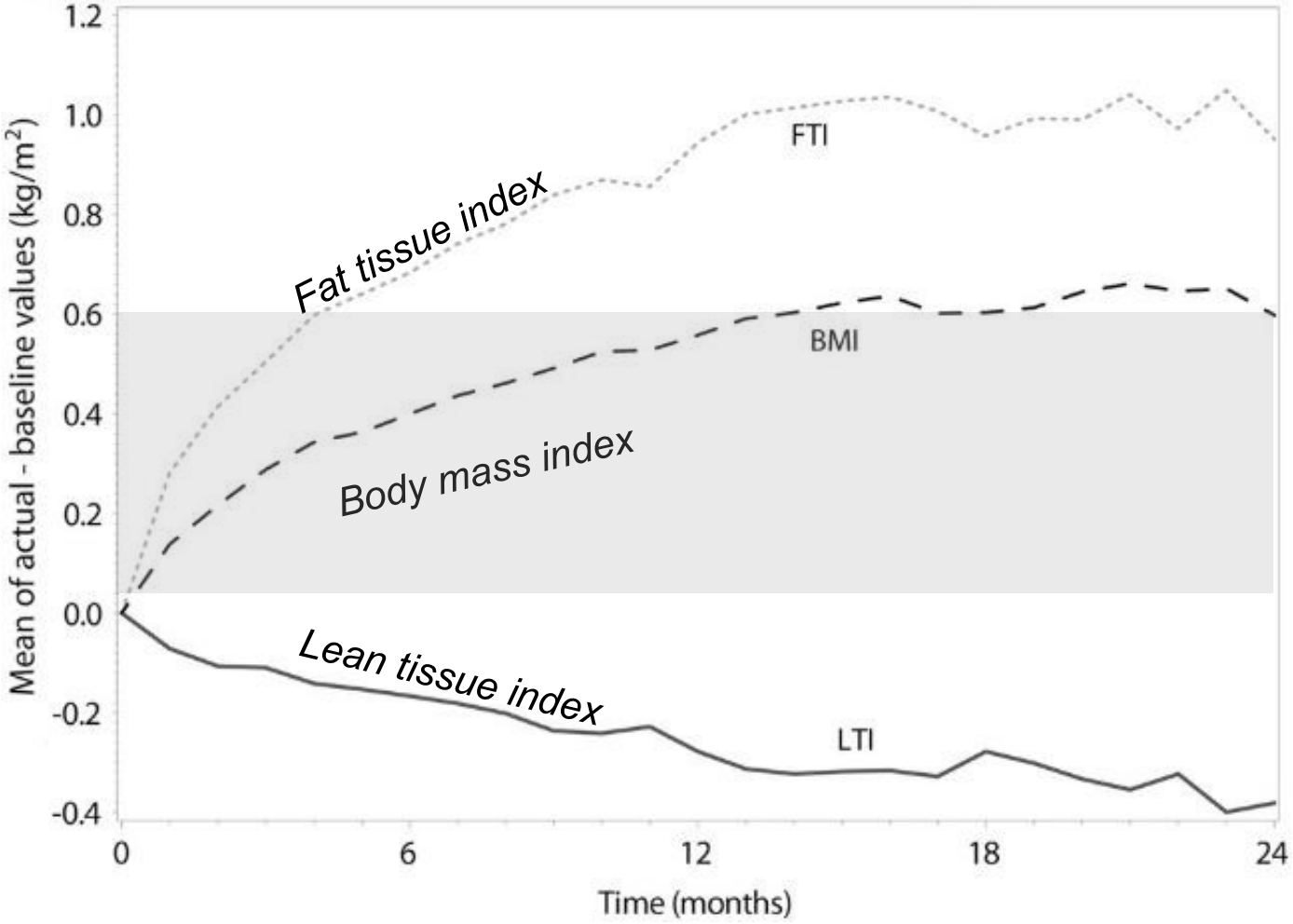
3. BMI does not differentiate **sex-differences in % fat**.

4. BMI does not differentiate **fat distribution** (central vs peripheral)

5. **Fluid overload** falsely increases BMI

ORIGINAL RESEARCH

Longitudinal Changes in Body Composition in Patients After Initiation of Hemodialysis Therapy: Results From an International Cohort



BMI can mask opposing changes in body composition

8227 incident HD patients undergoing repeated bioimpedance tests

Body composition provides much more clinically useful information than body size (BMI)

J Ren Nutr. 2016 Mar;26(2):72-80.

Nephrol Dial Transplant (2013) 28 (Suppl. 4): iv175–iv181
doi: 10.1093/ndt/gft024

ndt Nephrology Dialysis Transplantation

Original Articles

Subclinical versus overt obesity in dialysis patients: more than meets the eye

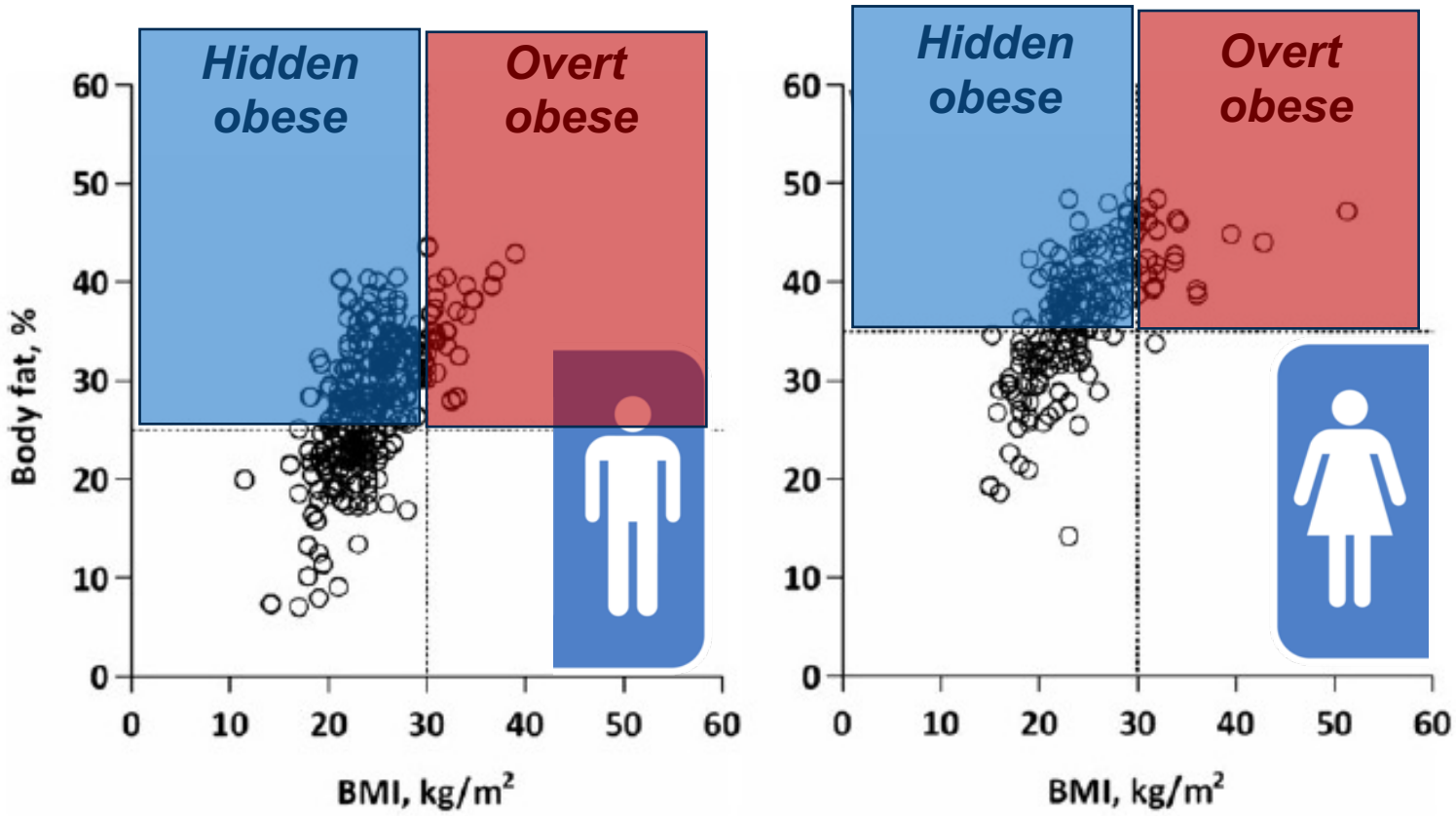
BMI missclassified
- **59% of obese men**
- **51% of obese women**

Approx. 500 dialysis patients from Stockholm

WHO obesity: as body fat % exceeding 25% in men and 35% in women.

Hidden obese individuals were more often malnourished and had both lower muscle mass and strength
OBESE SARCOPENIA

Overtly obese individuals had higher muscle mass and strength, and better nutritional status.



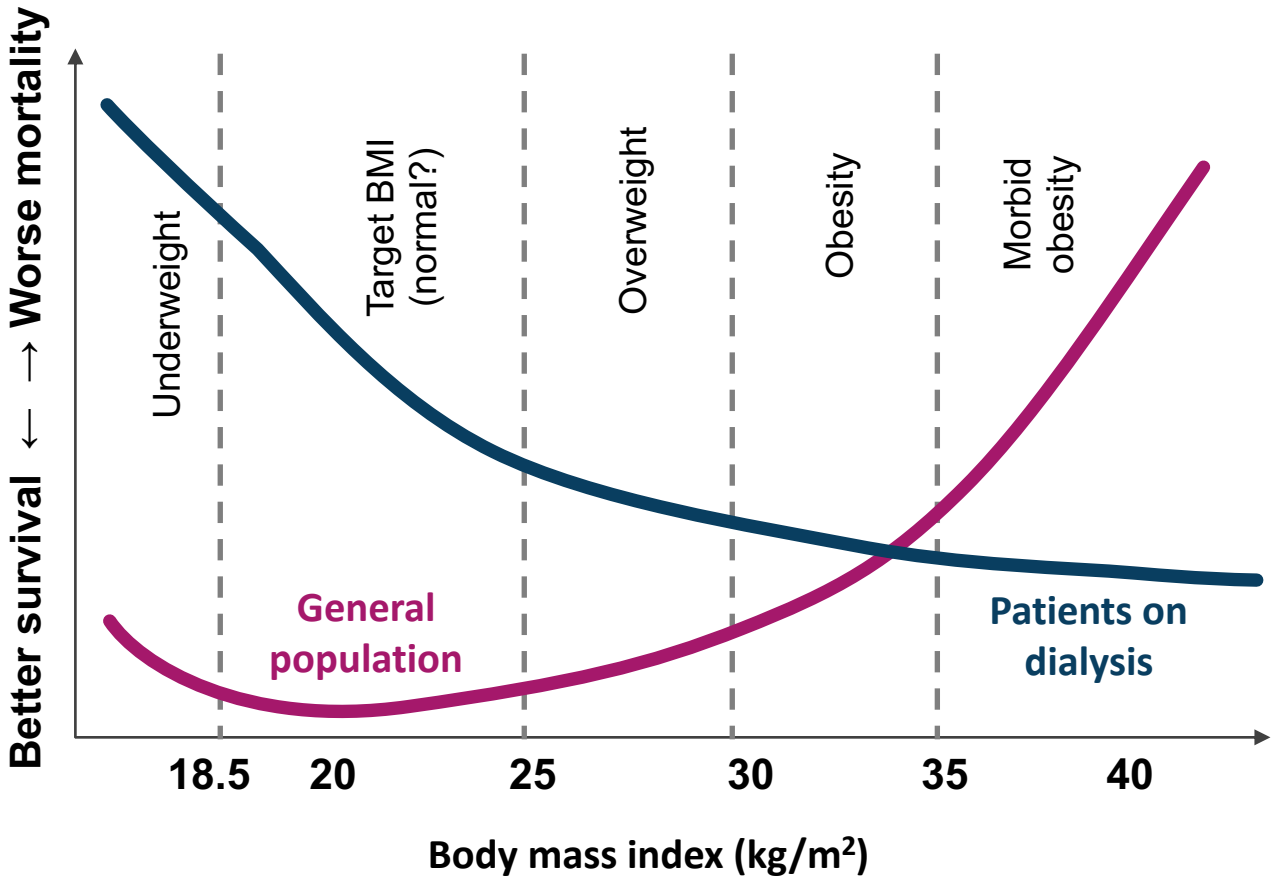
Nephrol Dial Transplant. 2013 Nov;28 Suppl 4:iv175-81.

What does a high-BMI represent in wasting-diseases like CKD?

- An overall marker of health
- An individual with more fat
- With more muscle, better bone density
- Better nutritional status

Someone with more energy stores to stand the process of wasting

THE OBESITY PARADOX EXPLAINED WITH COMPETING RISKS



BMI in wasting diseases represents energy abundance

Patients possibly die of the short-term consequences of protein-energy wasting,

not living long enough to die of the long-term consequences of obesity.

Kalantar-Zadeh K, et al. *Kidney Int Rep*. 2017;2(2):271-281.

MEASURES OF CENTRAL FATNESS ASSOCIATE MORE CONSISTENTLY THAN BMI WITH METABOLIC RISKS

OPEN ACCESS Freely available online PLoS one

Anthropomorphic Measurements That Include Central Fat Distribution Are More Closely Related with Key Risk Factors than BMI in CKD Stage 3

Philip D. Evans[1], Natasha J. McIntyre[1], Richard J. Fluck[1], Christopher W. McIntyre[1,2], Maarten W. Taal[1]*

1 Department of Renal Medicine, Royal Derby Hospital, Derby, United Kingdom, 2 Department of Vascular Medicine, The University of Nottingham, Derby Campus, Derby, United Kingdom

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doi:10.1016/j.jacc.2008.12.040

Obesity and CV Mortality in ESRD

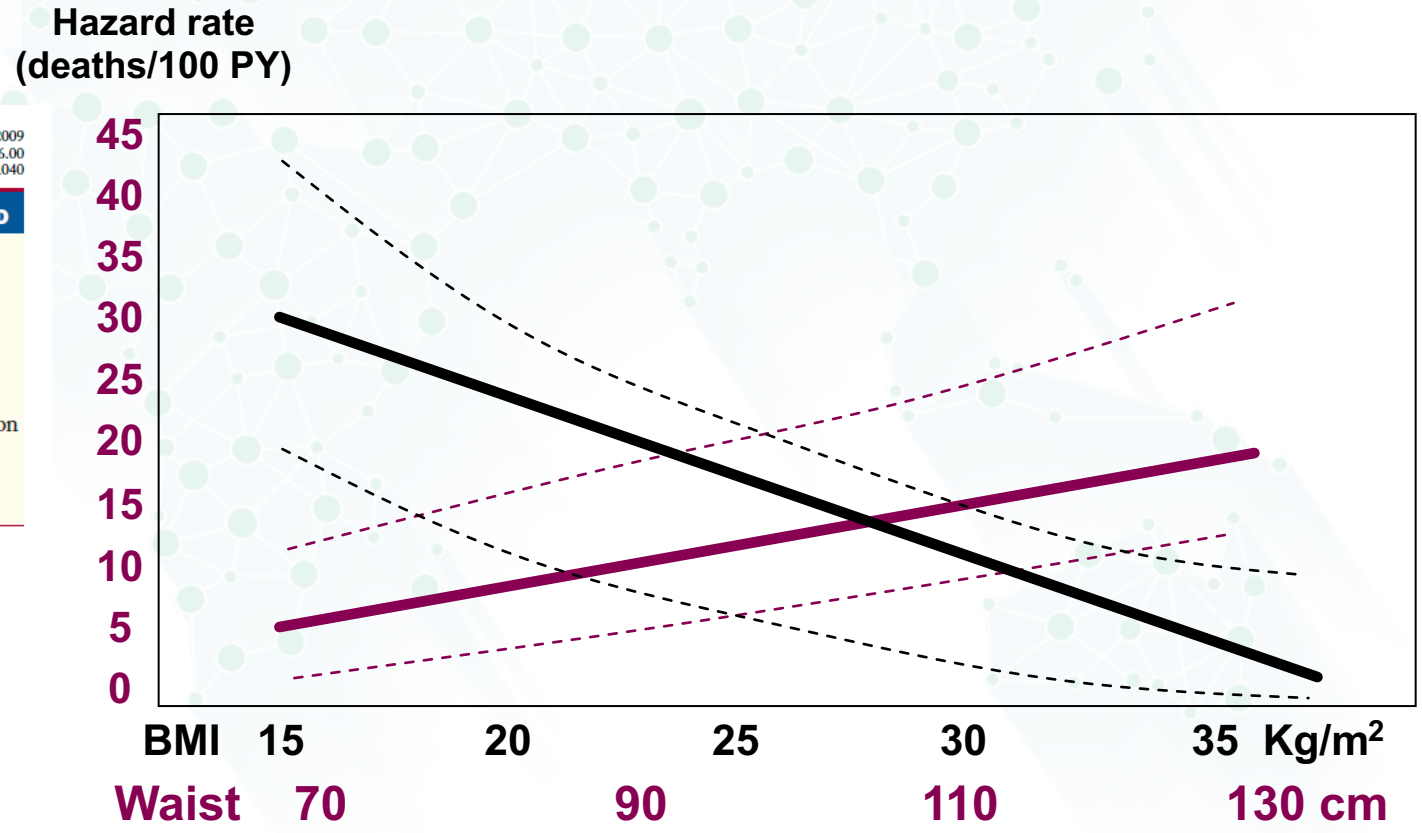
Abdominal Obesity and All-Cause and Cardiovascular Mortality in End-Stage Renal Disease

Maurizio Postorino, MD, Carmen Marino, TECH, Giovanni Tripepi, DRSTAT, Carmine Zoccali, PROF, on behalf of the CREDIT (Calabria Registry of Dialysis and Transplantation) Working Group

Reggio Calabria, Italy

J Am Coll Cardiol. 2009 Apr 14;53(15):1265-72.

1760 adults with CKD stage 3: **Stronger associations with blood pressure, hyperuricemia, arterial stiffness, albuminuria, inflammation**



BMI and abdominal fat estimations (WC) represent different risks:

- BMI is a marker of energy excess/health (muscle and fat).
- Waist circumference is a marker of obesity-associated risk

Moving away from body size to body composition in renal nutrition assessment

BMI

Insufficient to diagnose PEW, unless very low

(central) Fat stores:

- Waist circumference
- Conicity Index
- Skinfold thickness
- Bioimpedance

Muscle stores:

- Bioimpedance
- Handgrip strength
- Creatinine in dialysis

Screen for unintentional body weight loss

CKD stages	Frequency
CKD stages 1-3	At least annually
CKD stages 4-5 and Tx	Every 3 months
Dialysis	Monthly

KDOQI-AND *Nutrition Guidelines*.
Am J Kidney Dis. 2020 Sep;76(3 Suppl 1):S1-S107.

- Obesity leads to CKD and both conditions often coexist.
- Nephrology / transplantology can use more precise metrics of obesity for clinical decision making

@jjcarrero1

juan.jesus.carrero@ki.se