# OBESITY AS A KIDNEY DISEASE RISK FACTOR

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## AGENDA

- Epidemiology of obesity and kidney disease
- Mechanisms of kidney disease in obesity

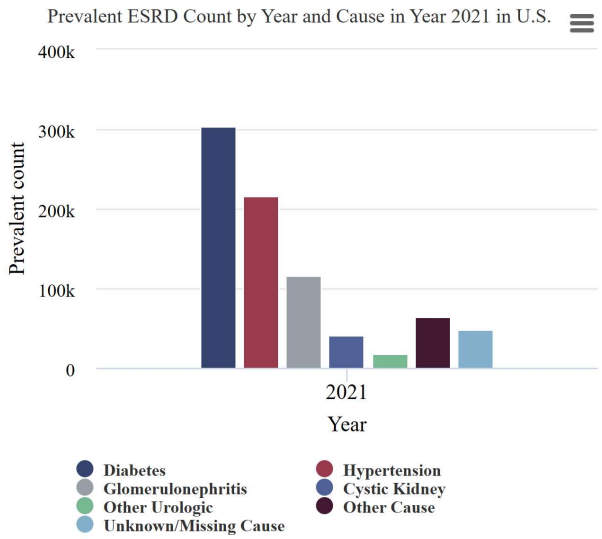
## DISCLOSURES

- Consulting for Bayer pharmaceuticals
- NKFI and NKF Board member

## QUESTION 1: WHAT PERCENTAGE OF KIDNEY DISEASE IS ATTRIBUTED AT LEAST IN PART TO OBESITY?

- A. 10%
- B. 25%
- C. 50%
- D. 60%

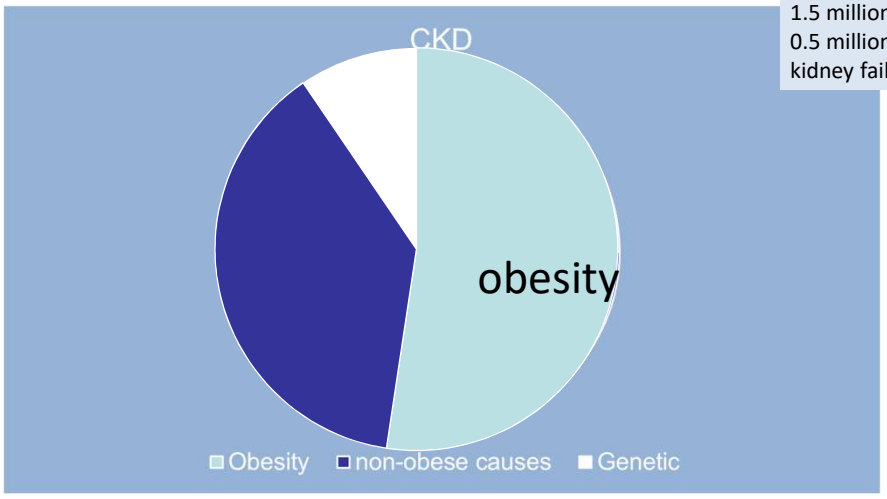
# Diabetes accounts for ~ 45% of kidney failure in U.S.




Usrds.org

# Obesity accounts for > 50% of CKD globally

Obesity, poor diet, low activity increases risk of diabetes

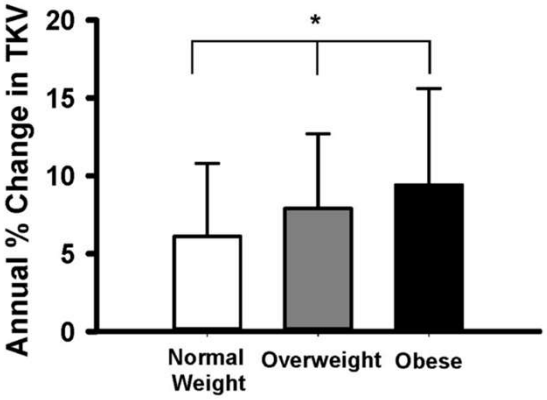



1.5 million deaths due to diabetes
0.5 million deaths due to diabetes with kidney failure globally annually

Friedman AN et al. JASN 2021; 32(4)777

Obesity contributing cause majority CKD

## Obesity accelerates genetic kidney disease progression




Nowak KL. J Am Soc Nephrol. 2018; 29:571

## Obesity accelerates genetic kidney disease progression

Associations ($\beta$ [95% confidence interval]) of BMI categories with eGFR slope

| Variable | Normal Weight (BMI 18.5–24.9 kg/m$^2$) ($n$=206) | Overweight (BMI 25–29.9 kg/m$^2$) ($n$=168) | Obese (BMI≥30 kg/m$^2$) ($n$=81) |
|---|---|---|---|
| Unadjusted | Ref | −0.03 (−0.08 to 0.03) | −0.08 (−0.15 to −0.02) |
| Model 1 | Ref | −0.03 (−0.08 to 0.02) | −0.09 (−0.15 to −0.02) |
| Model 2 | Ref | −0.02 (−0.07 to 0.03) | −0.08 (−0.14 to −0.01) |
| Model 3 | Ref | −0.03 (−0.08 to 0.03) | −0.08 (−0.14 to −0.02) |
| Model 4 | Ref | −0.02 (−0.08 to 0.03) | −0.08 (−0.15 to −0.02) |

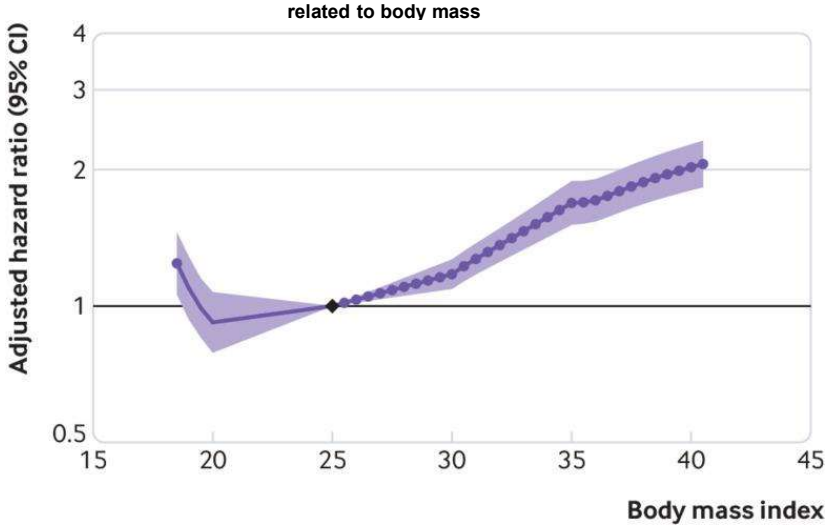
Model 1: adjusted for age, sex, race/ethnicity, and randomization group. Model 2: adjusted for model 1+randomization group and SBP. Model 3: Model 2+eGFR (CKD-EPI equation), urinary albumin excretion, and serum glucose. Model 4: model 3+mutation class. Mutation class is unavailable in $n$=11.

J Am Soc

**4-fold Faster decline in GFR with obesity in 441 adults with ADPKD, GFR > 60 baseline and no diabetes**

Nowak KL. J Am Soc Nephrol. 2018; 29:571

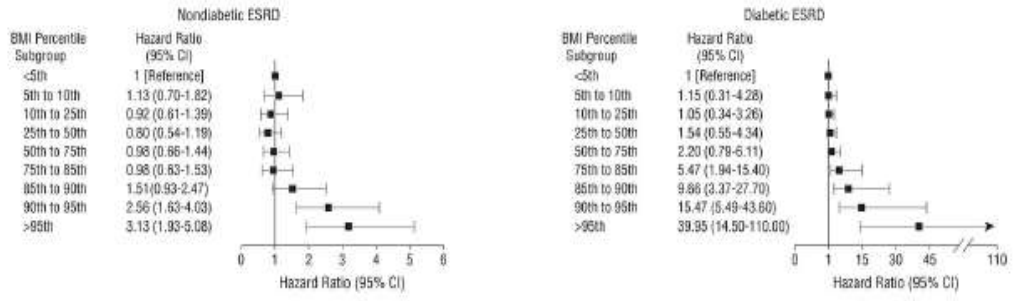
**Association between body mass index and risk of decline in glomerular filtration rate in general population cohorts, as shown by meta-analysed hazard ratios and 95% confidence intervals related to body mass**




Alex R Chang et al. BMJ 2019;364:bmj.k5301



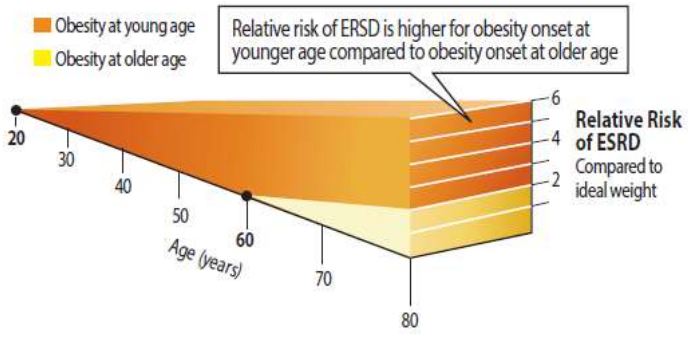
Obesity in adolescents strongly linked with lifetime risk of ESRD due to diabetes




Vivante A et al. Arch Intern Med. 2012; 172(21): 1644

# Adolescent with BMI ≥ 95th percentile

- 3-fold higher risk for kidney failure
- 40-fold higher risk for kidney failure due to diabetes




**2017-2020- Obesity among adolescents age 12-19 years 22.2%**

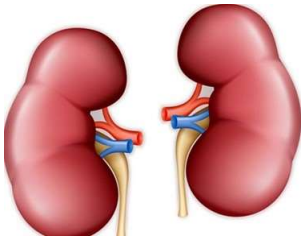
## Obesity among adolescents (age 10-17)

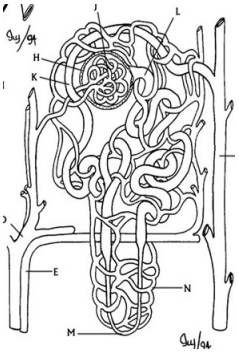
- IL 14.7% ranks 16/51
- AL 20.0%, ranks 41/51
- WV 24.8 ranks 51/51

## Question 2. How many nephrons on average in a healthy kidney?

- A. 100,000
- B. 300,000
- C. 500,000
- D. 800,000

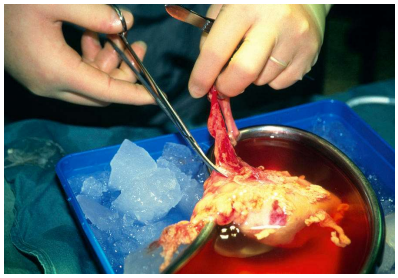
# Kidney resilience






Kidney failure is rare event

nephrons per kidney
Each nephron does not work
At maximal capacity in healthy
Non-obese state



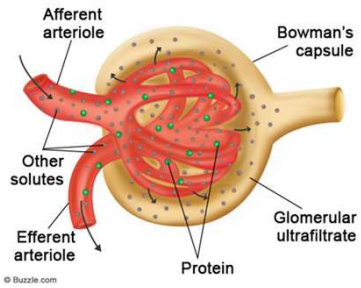
**Kidney Donation**

## Question 3. Who is at risk for CKD due to obesity?

- A. Reduced nephron number at birth
- B. Nephrectomy
- C. Kidney Disease
- D. Any of the above

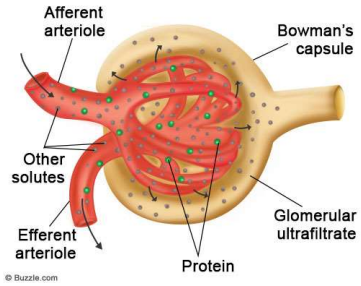
## Obesity and kidney disease
## Who is at risk?

- Reduced nephron number at birth
- Nephrectomy
- Kidney disease

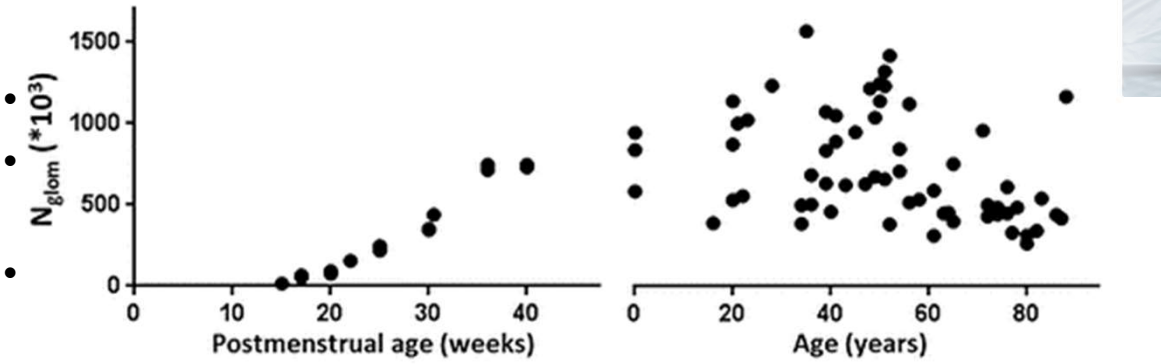


# Symmorphosis

- Glomerular filtration rate
- Renal Plasma flow




## *Factors affecting nephron number over a human's lifespan*




| Genetic | Prenatal (prematurity) | | Pediatric | Adult |
|---|---|---|---|---|
| RET | Nutrition | Tobacco | Nutrition | Diabetes |
| PAX2 | IUGR | Medications | AKI | Hypertension |
| ACE | Iron deficiency | -cyclosporine | Medications | Autoimmune diseases |
| OSR1 | Vitamin A deficiency | -ACEI | Chronic illnesses | UTI |
| ALDH1A2 | Vitamin D status | -NSAIDs | Hypertension | Urinary tract obstruction |
| | Hyperglycemia | -aminoglycosides | | AKI |
| | Ethanol | | | Medications |

016

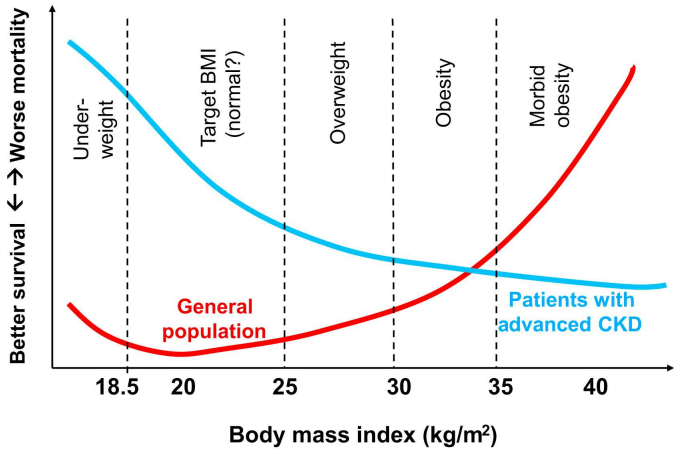
J.R. Charlton. Pediatric Nephrology. 2014; 29:2299

Autopsies of adults show wide variation in nephron number

**200,000 to 2 million nephrons**
**10-fold difference in CKD vulnerability**

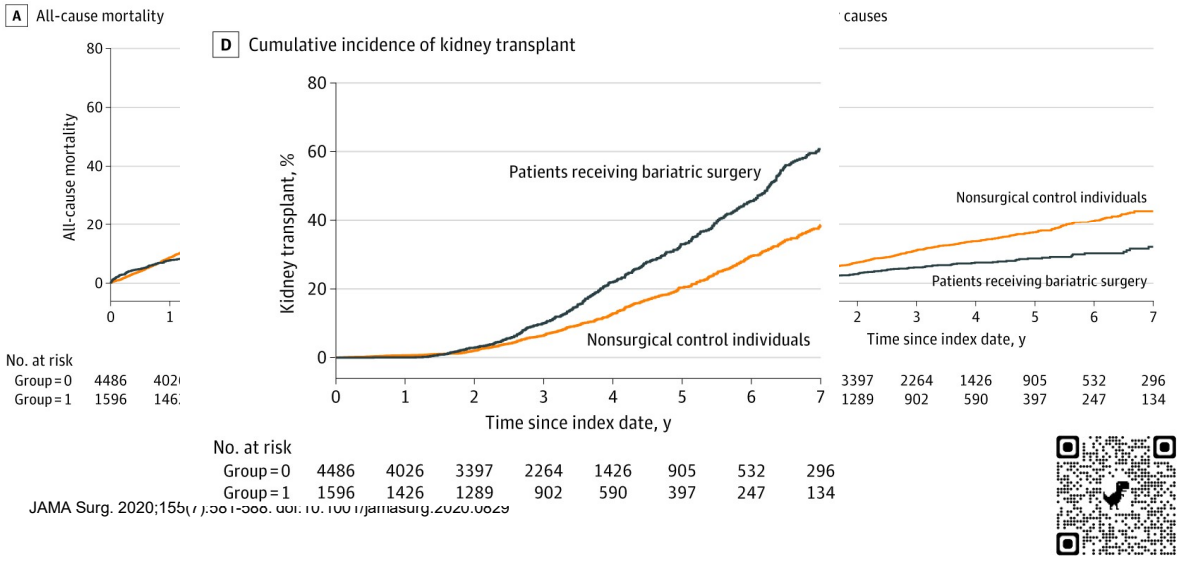
Is obesity always bad?

# Obesity paradox




*K Kalantar-Zadeh et al. Kidney International Reports* 2017 2271-281DOI: (10.1016/j.ekir.2017.01.009)

# Comparison of 1597 adults with ESKD who underwent bariatric surgery vs. 1597 age-matched patients with ESKD who did not

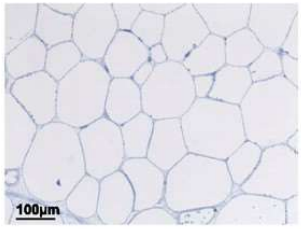



JAMA Surg. 2020;155(7):561-568. doi:10.1001/jamasurg.2020.0629

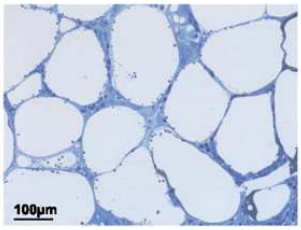
# Is all adipose tissue bad?

A

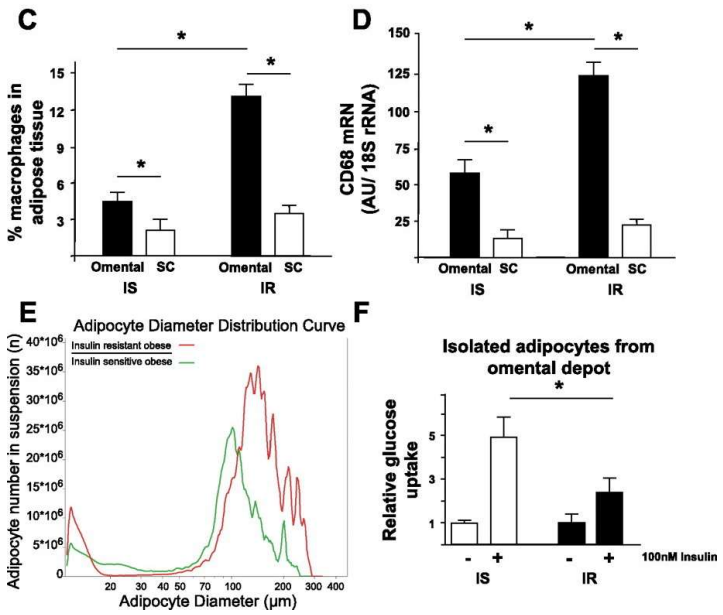
Insulin sensitive




Insulin resistant




N. Kloting et al. Am J Physiol 2010.




Insulin resistant obese in red
Insulin sensitive obese in green

N. Kloting et al. Am J Physiol 2010

# Obesity is stressful on the kidney

Question 4: The increase in renal blood flow and glomerular filtration rate in nephrons in the setting of obesity leads to what types of stress in the kidney?

- A. Tensile stress
- B. Shear stress
- C. Stress on podocytes
- D. All of the above

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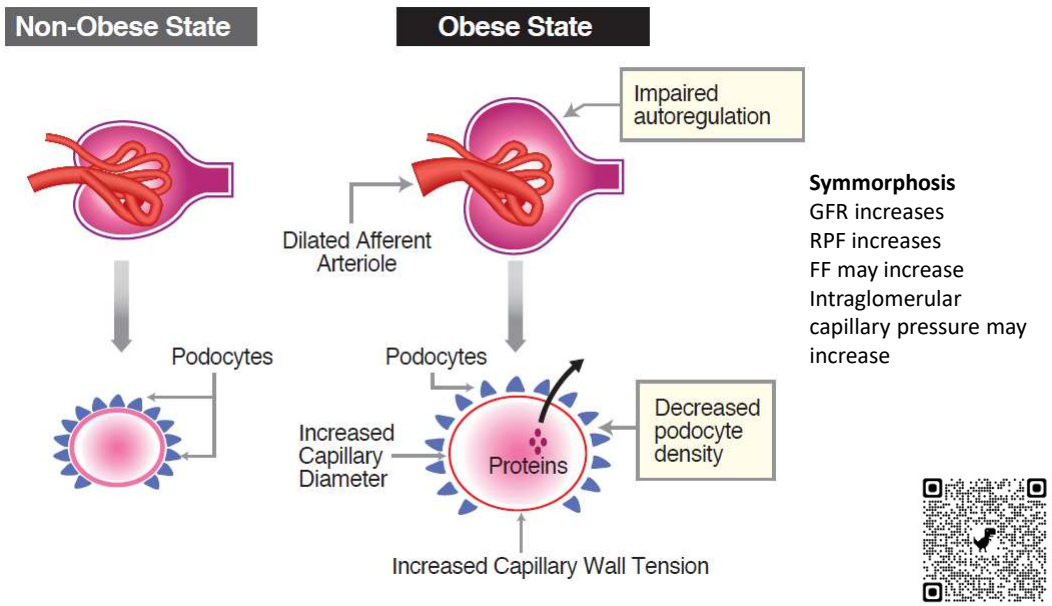
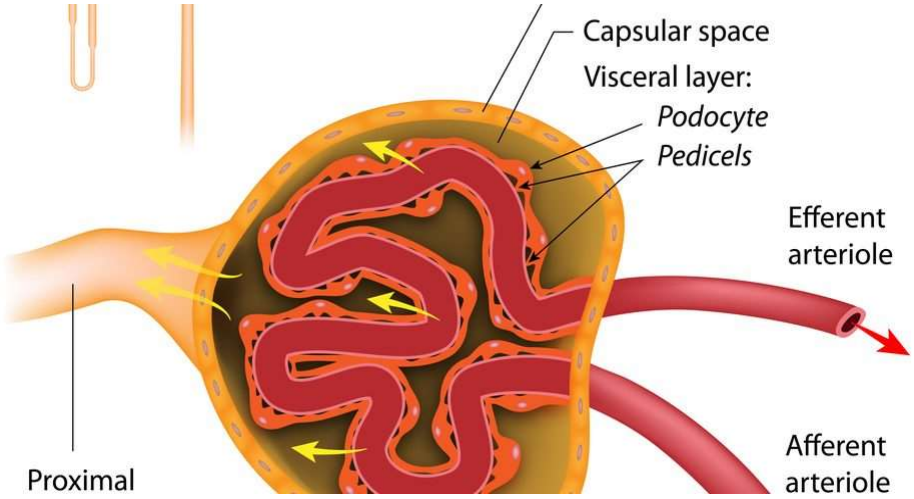
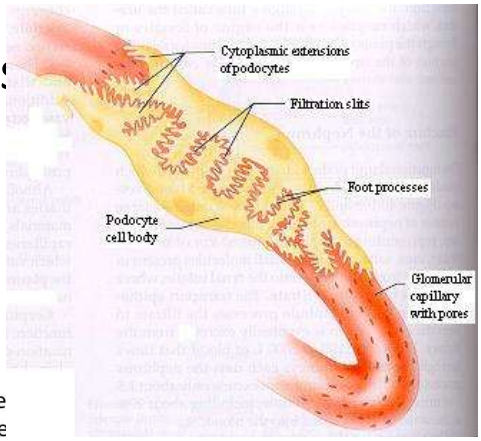


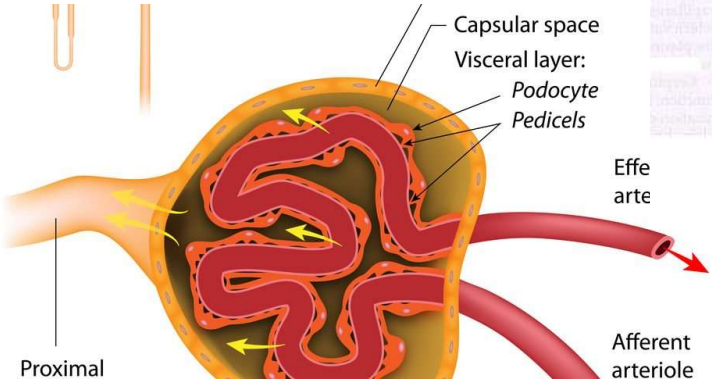

NOS Camara, H. Kramer et al Nature Reviews Nephrology. 2017; 13:181-190

Glomerular capillary length and area increases due to increased tensile stress




Shear stres




24-Apr-24

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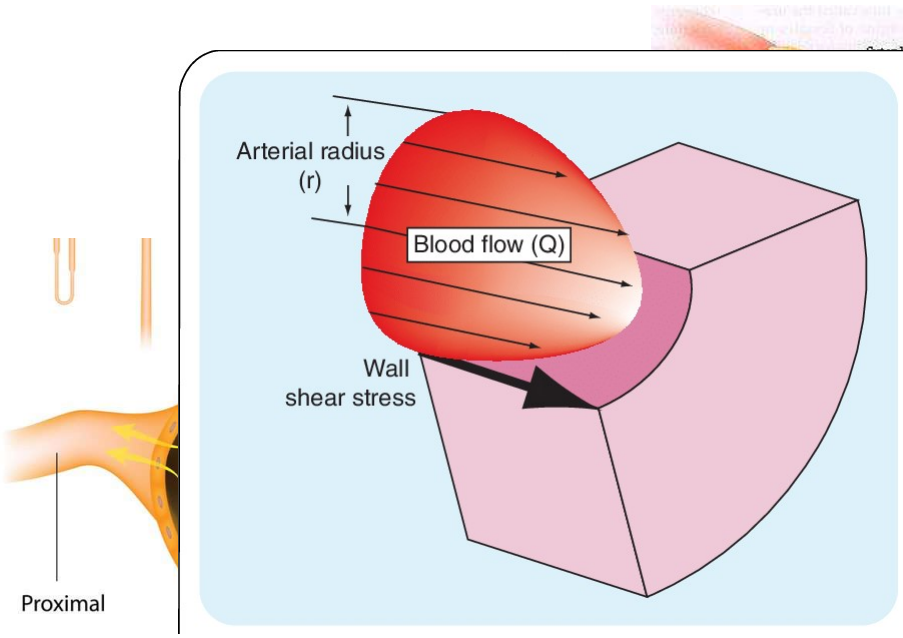


NOS Camara, H. Kramer et al Nature Reviews Nephrology. 2017; 13:181-190

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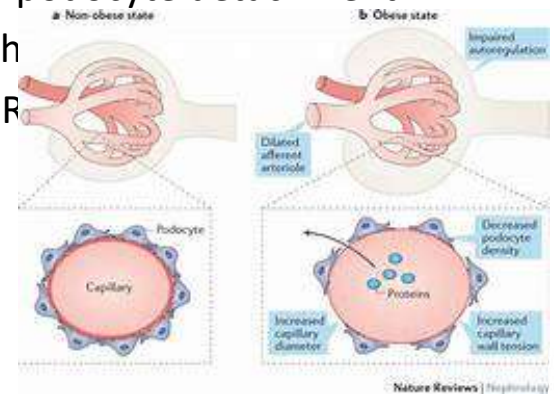
# Mechanical Stress

- Mechanical stress leads to podocyte detachment
- Activation of signaling path
- Angiotensin II, mTOR, TGFR




24-Apr-24

N. Camara. Nature Reviews Nephrology 2017

## Obesity

- Cardiac output increases due to increased stroke volume and higher heart rate
- Increased sodium delivery to kidneys
- Activation of renin-angiotensin system-increases sodium avidity
- Insulin resistance---increased glucose delivery to proximal tubule

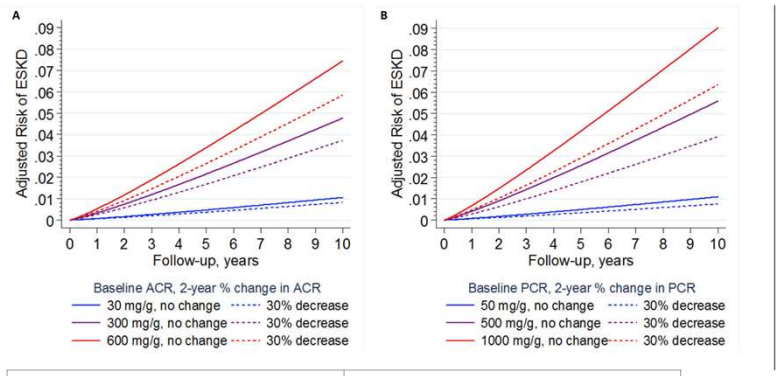
# Impact of weight management on CKD progression

## Question 5. How does change in albuminuria correlate with kidney failure risk?

- A. The higher the baseline urine albumin excretion, the higher the kidney failure risk
- B. A 30% decline in urine albumin excretion is associated with reduced risk of kidney failure
- C. The higher the baseline urine albumin excretion, the greater the reduction in risk of kidney failure with reduction in urine albumin excretion
- D. All of the above

## Risk of kidney failure by change in albuminuria

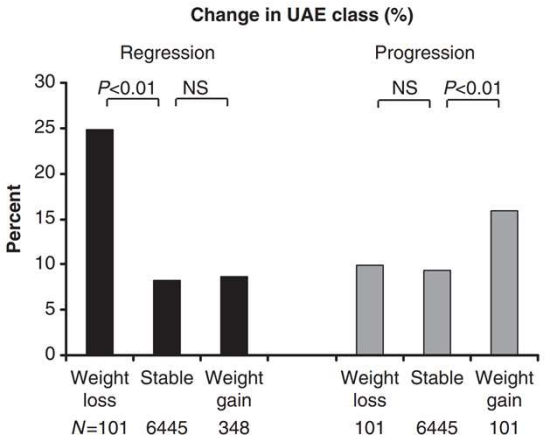
28 cohorts, 693, 816 persons, 7461 kidney failure events




| | |
|---|---|
| 30% reduction UACR at 1 year | 25% relative risk reduction kidney failure (95% CI: 0.13%, 34%) |

Coresh J. et al. Lancet Diabetes Endocrinology 2019; 7(2): 115

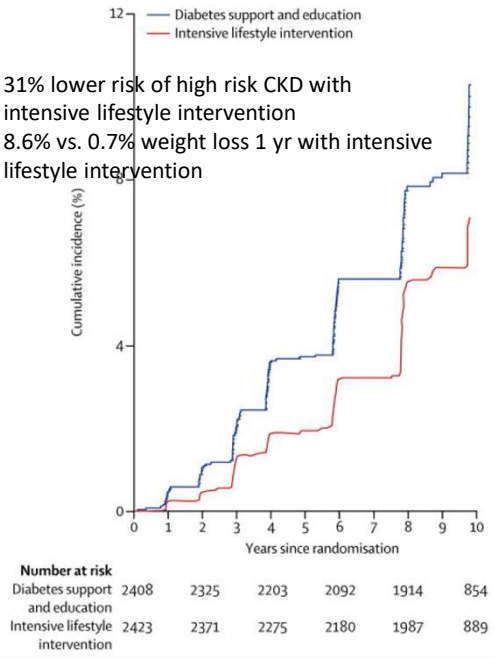
# Weight loss associated with reduction in albuminuria: 6894 PREVEND participants, 4 yr fu

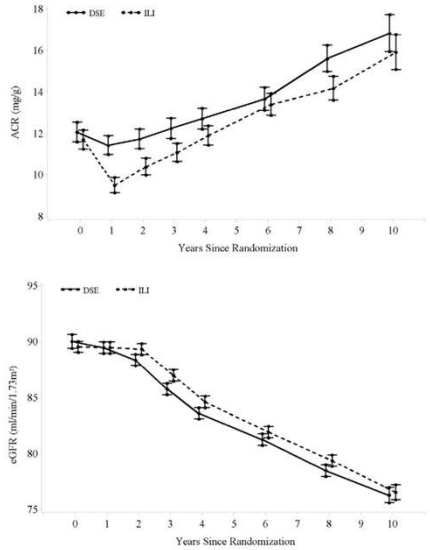



AK Bello et al. NDT 2007; 22: 1619

# Look AHEAD Trial

31% lower risk of high risk CKD with intensive lifestyle intervention
8.6% vs. 0.7% weight loss 1 yr with intensive lifestyle intervention




Lancet Diabetes & Endocrin 2014; 2(10): 801

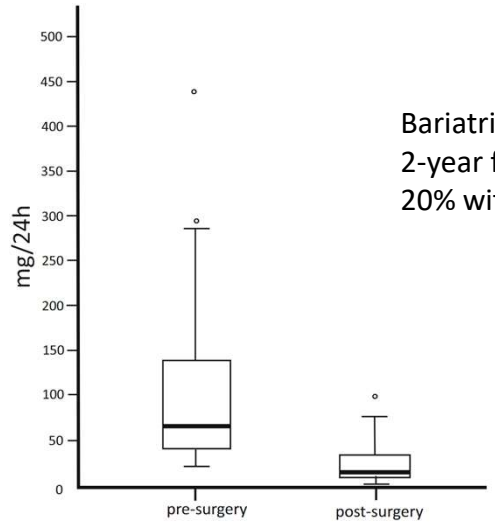



Fig. 2 Decrease of albuminuria after bariatric surgery in patients with preoperative albuminuria

Bariatric surgery reduces urine albumin excretion
2-year follow-up 318 adults (mean age 40 years)
20% with diabetes

JM Brix et al. Obes Surg 2019; 29(11): 3581

# Medications for weight loss

| Drug | CKD stage 3-5 | ESKD |
|---|---|---|
| Orlistat | NR | NR |
| Phenteremine | GFR 15-29 reduced dose | NR |
| Phenteremine/topiramate | Reduced dose | NR |
| Bupropion-Naltrexone | Reduced dose with CKD stage 4-5 | NR |

AN Friedman et al. JASN 2021: 32(4): 777

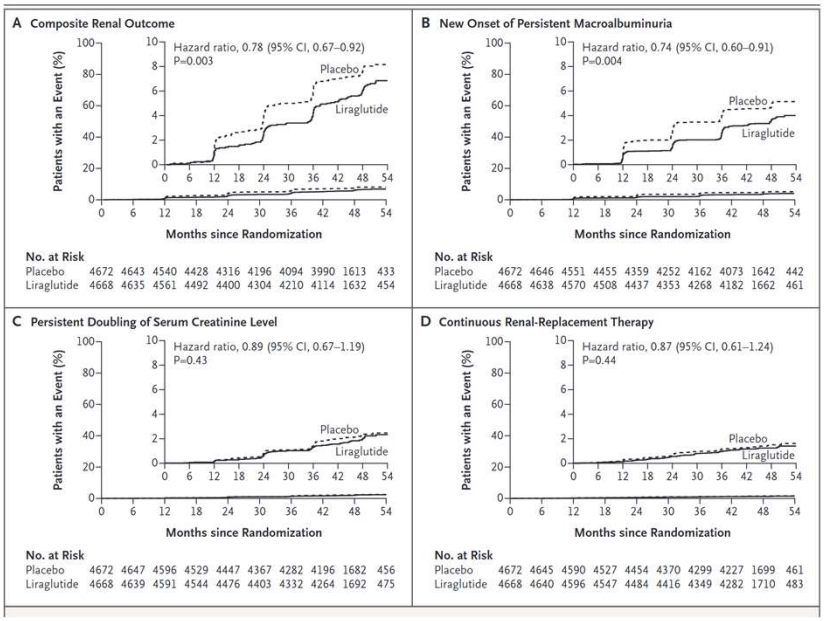
# GLP1 Receptor Agonists

| GLP1 receptor agonists | Renal license limitation |
|---|---|
| Exenatide BD (Byetta) | |
| | eGFR 30-50 ml/min—use with caution |
| | eGFR < 30 ml/min—not recommended |
| Exenatide QW (Bydureon) | eGFR < 50 ml/min—not recommended |
| Lixisenatide (Lyxumia) | eGFR < 30 ml/min—not recommended |
| Liraglutide (Victoza) | eGFR < 15 ml/min—not recommended |
| Dulaglutide (Trulicity) | eGFR < 15 ml/min—not recommended |
| Semaglutide (Ozempic) | eGFR < 15 ml/min—not recommended |

*eGFR* estimated glomerular filtration rate

Decrease body weight by 10-16% after one year

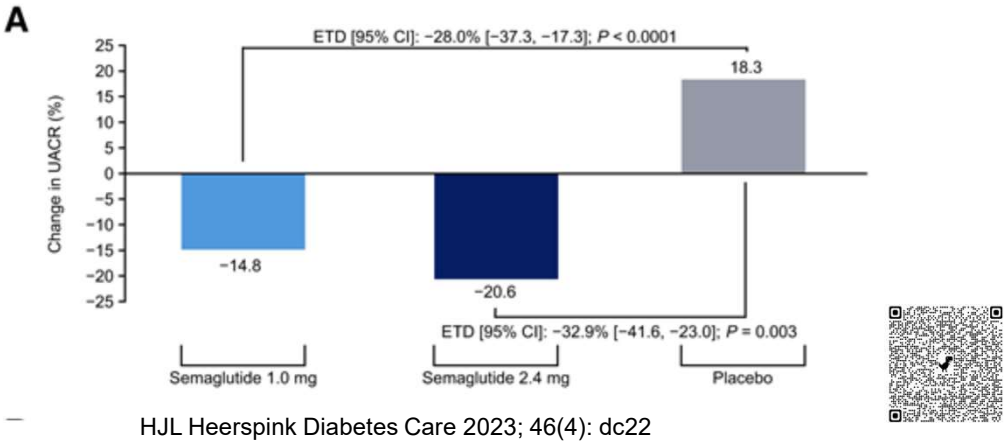
WL Yin Diab Ther 2020; 11(4): 835



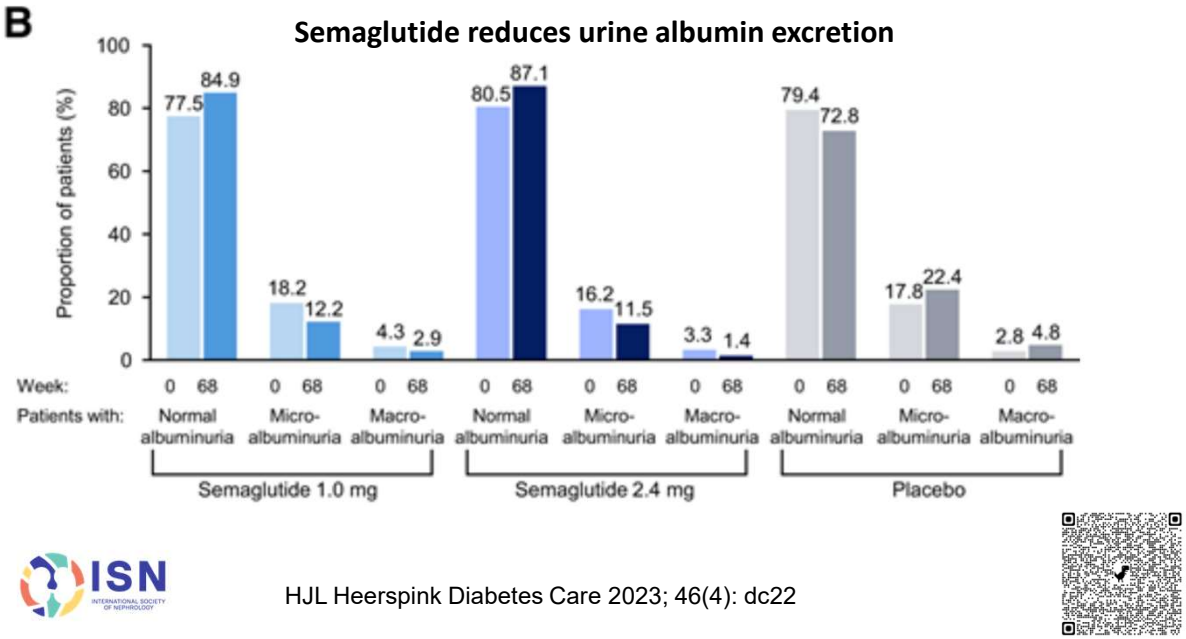

Composite renal outcome: Persistent macroalbuminuria, doubling serum creatinine eGFR < 45 ml/min, dialysis, death due to kidney failure

JFE Mann NEJM 2017; 377:9

## Step 1-3 trials -Semaglutide use associated with reduction in albuminuria

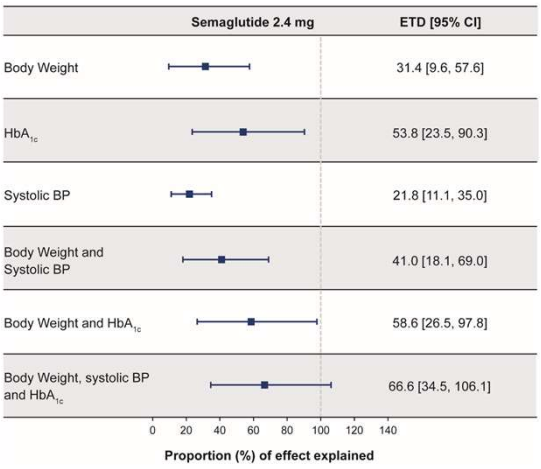



HJL Heerspink Diabetes Care 2023; 46(4): dc22



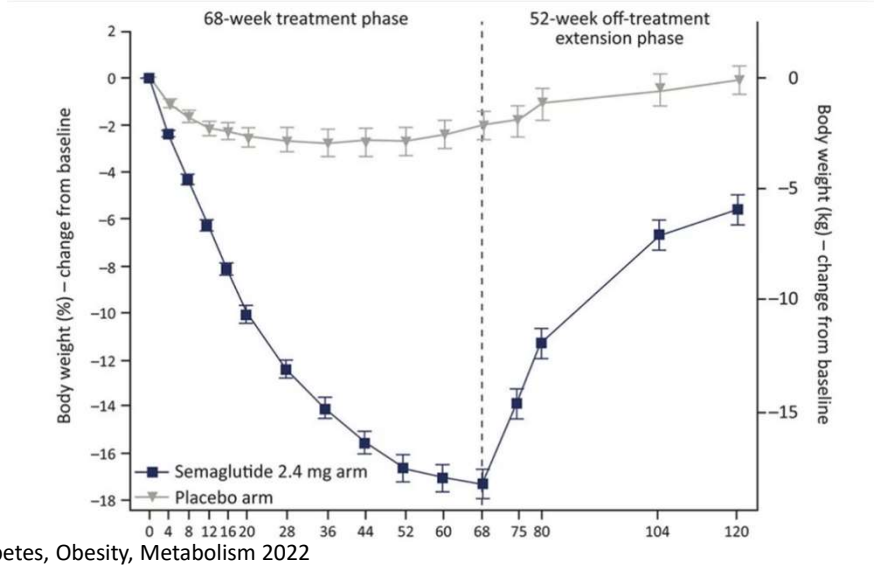

HJL Heerspink Diabetes Care 2023; 46(4): dc22

**Figure S3—Mediation analysis of $HbA_{1c}$, body weight, and systolic blood pressure; semaglutide 2.4 mg dose (STEP 2)**



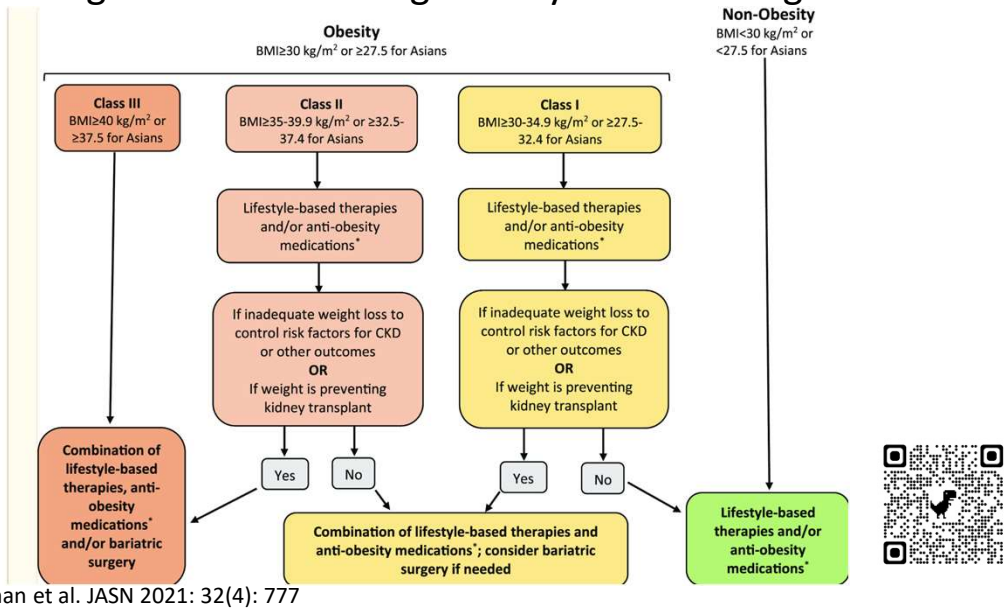

HJL Heerspink Diabetes Care 2023; 46(4): dc22

## Step 1 Study. 1961 adults with BMI ≥ 30 kg/m$^2$




Wilding JPH. Diabetes, Obesity, Metabolism 2022
DOI: 10.1111/dom.14725

## Suggested algorithm for treating obesity in the setting of CKD




AN Friedman et al. JASN 2021: 32(4): 777

Thank you