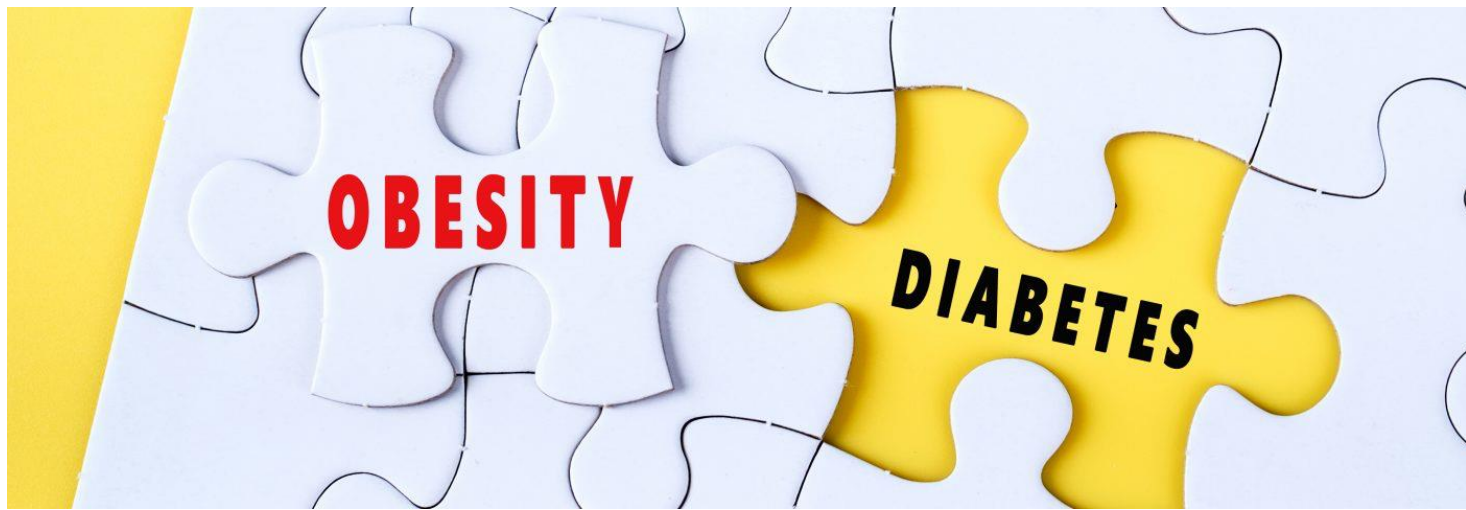


# Early Detection of CKD: Diabetes and Obesity



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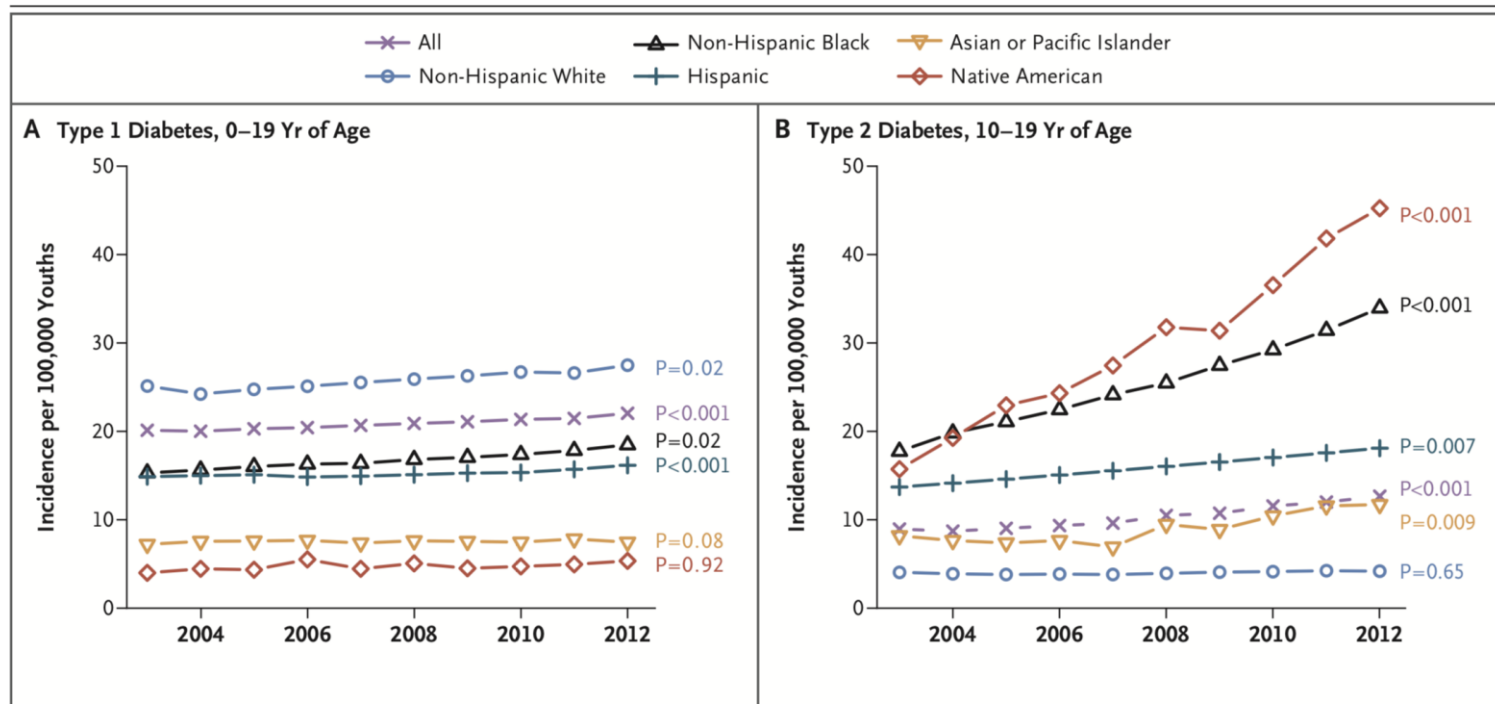
# Objectives

- ▶ Describe the impact of diabetes and obesity in the pediatric population
- ▶ Discuss early markers of renal disease in diabetes and obesity
- ▶ Propose evidenced-based management options to slow progression of renal disease in children with diabetes and obesity

# Diabetic Kidney Disease Facts

- The progression of kidney disease in type 1 diabetes mellitus seems to be connected to control of blood sugar and Blood Pressure
- 80% microalbuminuric patients progress to proteinuria over 6–14 years
  - Recent studies have reported a regression as a result of better glycemic control

# Incidence Trends DM Children



**Figure 1. Model-Adjusted Incidence Estimates.**

Shown are model-adjusted incidence estimates per 100,000 youths. The incidence of type 1 diabetes was assessed among participants who were 0 to 19 years of age, and the incidence of type 2 diabetes among participants who were 10 to 19 years of age. P values are for the linear trend tests in each racial or ethnic group, according to type of diabetes. Significant results suggest a positive annual rate of increase during the study period.

# Diabetes Type I vs II in Children

**Table 3.** Proportional Distribution of Type 1 and Type 2 DM (2002-2003) by Age Group at Diagnosis and Race/Ethnicity

DM	No. (%) of Youth									
	0-9 y					10-19 y				
	Non-Hispanic White	African American	Hispanic	Asian/Pacific Islander	American Indian	Non-Hispanic White	African American	Hispanic	Asian/Pacific Islander	American Indian
Type 1	660 (99.4)	89 (93.7)	102 (95.3)	26 (86.7)	7 (100)	749 (85.1)	114 (42.2)	116 (53.9)	30 (30.3)	9 (13.8)
Type 2	4 (0.6)	6 (6.3)	5 (4.7)	4 (13.3)	0	132 (14.9)	156 (57.8)	99 (46.1)	69 (69.7)	56 (86.2)
<b>Total</b>	<b>664 (100)</b>	<b>95 (100)</b>	<b>107 (100)</b>	<b>30 (100)</b>	<b>7 (100)</b>	<b>881 (100)</b>	<b>270 (100)</b>	<b>215 (100)</b>	<b>99 (100)</b>	<b>65 (100)</b>

Abbreviation: DM, diabetes mellitus.

*JAMA 2007;297:2716-2724*

# KDOQI DKD Guideline 1

## *Screening and Diagnosis of DKD*

- CKD in patients with DM may or may not represent DKD. In the absence of an established diagnosis, the evaluation of patients with diabetes and kidney disease should include investigation into the underlying cause(s).
  - 1.1 Patients with diabetes should be screened annually for DKD. Initial screening should commence:
    - 5 years after the diagnosis of type 1 diabetes
    - From diagnosis of type 2 diabetes
  - 1.1.1 Screening should include:
    - Measurements of urinary albumin/creatinine ratio (ACR) in a spot urine sample;
    - Measurement of serum creatinine and estimation of GFR

# KDOQI DKD Guideline 1

- 1.2 An elevated ACR should be confirmed in the absence of UTI with 2 additional first-void specimens collected over the next 3 to 6 months
  - Microalbuminuria is defined as an ACR between 30–300 mg/g
  - Macroalbuminuria is defined as an ACR  $> 300$  mg/g
  - 2 of 3 samples should fall within the microalbuminuric or macroalbuminuric range to confirm classification
- 1.3 In most patients with diabetes, CKD should be attributable to diabetes if:
  - Macroalbuminuria is present
  - Microalbuminuria is present
    - in the presence of diabetic retinopathy
    - in type 1 diabetes of at least 10 years' duration

# KDOQI Guideline 1

- 1.4 Suspect Non-DKD if....

- Absence of diabetic retinopathy;
- Low or rapidly decreasing GFR;
- Rapidly increasing proteinuria or nephrotic syndrome;
- Refractory hypertension;
- Presence of active urinary sediment;
- Signs or symptoms of other systemic disease; or
- >30% reduction in GFR within 2-3 months after initiation of an ACE inhibitor or ARB.

Reproduced with permission of NKF from KDOQI diabetes and CKD guideline.<sup>4</sup>


Am J Kidney Dis. 2014;64(4):510-533




# KDOQI Guideline 2

- *2. Management of Hyperglycemia and General Diabetes Care in CKD*
  - Hyperglycemia, the defining feature of DM, is a fundamental cause of vascular target-organ complications, including kidney disease.
  - Intensive treatment of hyperglycemia prevents DKD and may slow progression of established kidney disease.
    - 2.1 Target HbA1c for people with diabetes should be  $< 7.0\%$ , irrespective of the presence or absence of CKD

# KDOQI DKD Guideline 3

- **Most people with diabetes and CKD have hypertension. Treatment of hypertension slows the progression of CKD.**
    - **3.1 Hypertensive people with diabetes and CKD stages 1–4 should be treated with an ACE inhibitor or an ARB, usually in combination with a diuretic**
    - **3.2 Target blood pressure in diabetes and CKD stages 1–4 should be < 130/80 mm Hg**
- 

# Clinical Practice Recommendation 1

- Treatments that lower urinary albumin excretion may slow progression of DKD and improve clinical outcomes, even in the absence of hypertension. However, most people with diabetes and albuminuria have hypertension; management of hypertension in these patients is reviewed in Guideline 3.
    - 1.1 Normotensive people with diabetes and macroalbuminuria should be treated with an ACE inhibitor or an ARB
    - 1.2 Treatment with an ACE inhibitor or an ARB may be considered in normotensive people with diabetes and microalbuminuria
    - 1.3 Albuminuria reduction may be considered a treatment target in DKD
- 

# KDOQI Guideline 4

- ***4. Management of Dyslipidemia in DM and CKD***
  - Dyslipidemia is common in people with DM and CKD
  - The risk of CVD is greatly increased in this population
  - People with DM and CKD should be treated according to current guidelines for high-risk groups
    - 4.1 Target low-density lipoprotein cholesterol (LDL-C) in people with diabetes and CKD stages 1–4 should be < 100 mg/dL; <70 mg/dL is a therapeutic option
    - 4.2 People with diabetes, CKD stages 1–4, and LDL-C > 100 mg/dL should be treated with a statin
    - 4.3 Treatment with a statin should not be initiated in patients with type 2 diabetes on maintenance hemodialysis therapy who do not have a specific cardiovascular indication for treatment

# KDOQI Guideline 5

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No protein restriction in  
growing children  
Negative effects on  
growth



# Diabetic Kidney Disease in Children

- CKD stage 3 or greater due to DKD is rare in children and adolescents
- Also, children and adolescents are more likely to revert from microalbuminuria to normoalbuminuria than adults
- Data regarding treatment of hyperglycemia, hypertension, and dyslipidemia in children with diabetes and adolescents with CKD are almost nonexistent.



# Glucose Control in Children

**Table 51. Plasma Blood Glucose and HbA<sub>1c</sub> Goals for Type 1 Diabetes by Age Group**

Values by age (y)	Plasma Blood Glucose Goal Range (mg/dL)		HbA <sub>1c</sub> (%)	Rationale
	Before Meals	Bedtime/Overnight		
Toddlers and preschoolers (<6)	100-180	110-200	≤8.5 (but ≥ 7.5)	<ul style="list-style-type: none"> <li>• High risk and vulnerability to hypoglycemia</li> </ul>
School age (6-12)	90-180	100-180	<8	<ul style="list-style-type: none"> <li>• Risk of hypoglycemia and relatively low risk of complications before puberty</li> </ul>
Adolescents and young adults (13-19)	90-130	90-150	<7.5*	<ul style="list-style-type: none"> <li>• Risk of hypoglycemia</li> <li>• Developmental and psychological issues</li> </ul>

Key concepts in setting glycemic goals:

- Goals should be individualized and lower goals may be reasonable based on benefit-risk assessment
- Blood glucose goals should be higher than those listed in children with frequent hypoglycemia or hypoglycemia unawareness
- Postprandial blood glucose values should be measured when there is a disparity between preprandial blood glucose values and HbA<sub>1c</sub> levels


\*A lower goal (<7.0%) is reasonable if it can be achieved without excessive hypoglycemia

Reprinted with permission.<sup>174</sup>

# Strategies to Delay Progression


- Intensive glycemic control
- Antihypertensive treatment by blocking RAAS system
  - Consider treating microalbuminuria, even if normotensive
- Lipid-modifying statin therapy



A photograph of a person's midsection, showing their waist and hips. They are wearing blue jeans. A pink measuring tape is wrapped around their waist, and a hand is holding the end of the tape. The background is a solid teal color.

# **The relation between Kidney Disease and Obesity**

# Obesity Facts – WHO 2016

- 41 million children < 5 y/o are overweight or obese
  - >340 million children 5–19 y/o are overweight or obese
  - Once considered a high-income country problem, overweight and obesity are now on the rise in low- and middle-income countries, particularly in urban settings.
    - Africa
      - the number of overweight children under 5 has increased by nearly 50% since 2000.
  - The prevalence of overweight and obesity among children and adolescents aged 5–19 y/o has risen from 4% in 1975 to > 18% in 2016.
    - The rise has occurred similarly among both boys and girls: in 2016 18% of girls and 19% of boys were overweight.
  - While just under 1% of children and adolescents aged 5–19 were obese in 1975, 6% of girls and 8% of boys were obese in 2016.
- 

# Kidney Disease and Obesity

HEALTHY LIFESTYLE FOR HEALTHY KIDNEYS

9 March 2017



© <http://www.kidney.org>

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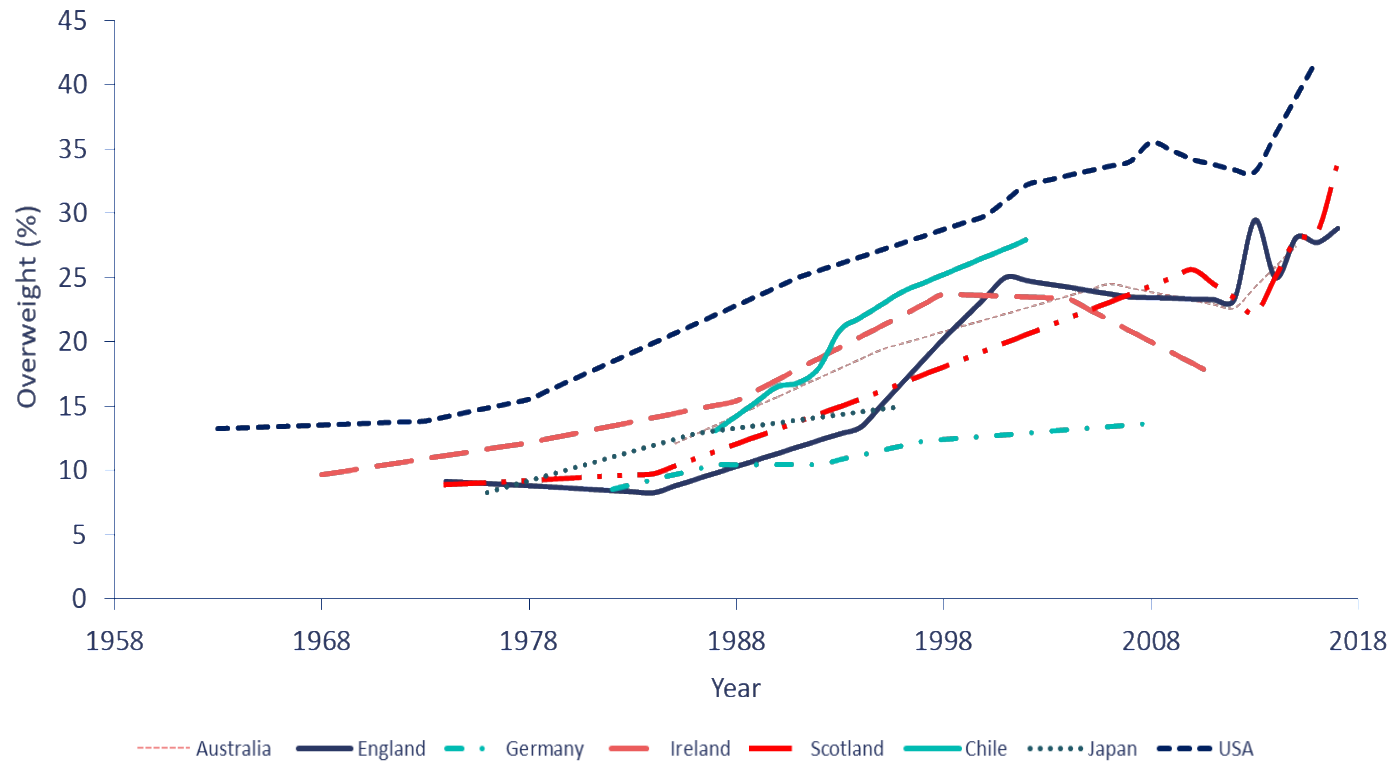
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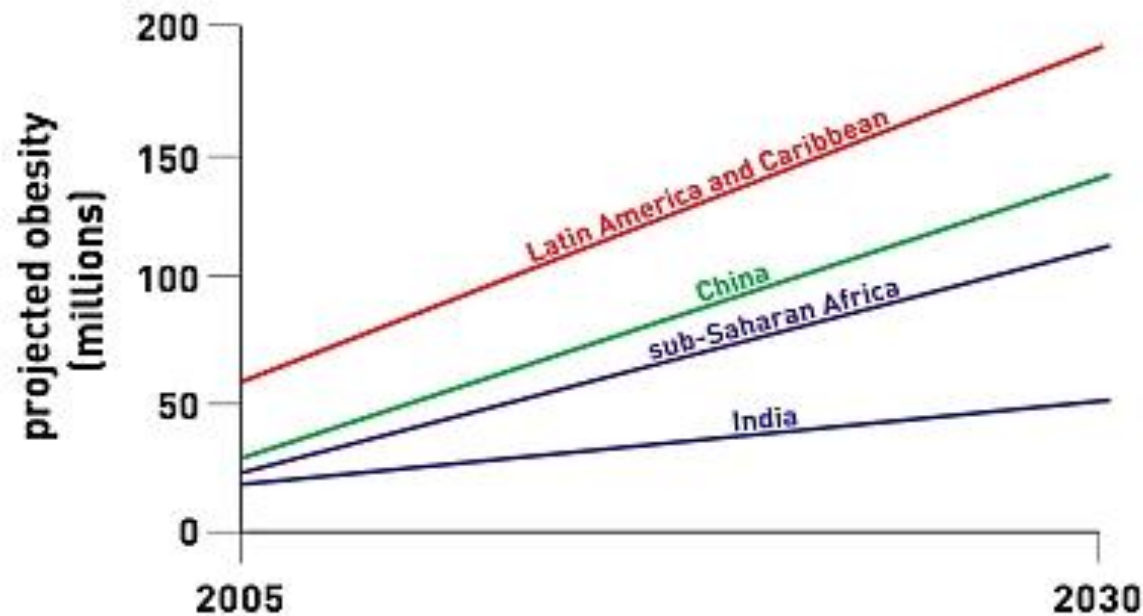


Changes in % child overweight prevalence over time in selected countries worldwide



©World Obesity Federation, December 2018

## LATIN AMERICA HAS THE WORST SCENARIOS OF OBESITY FOR COUNTRIES IN EMERGING REGIONS BY 2030.



Source: The World Bank, Food Price Watch, March 2013.



# Risk of Adult Obesity





# Overweight: Independent Risk Of CKD

Table 4. OR for CRF associated with BMI<sup>a</sup>

	No Diabetes		No Hypertension		No Diabetes or Hypertension	
	No. of Case Patients/Control Subjects	OR <sup>b</sup> (95% CI)	No. of Case Patients/Control Subjects	OR <sup>b</sup> (95% CI)	No. of Case Patients/Control Subjects	OR <sup>b</sup> (95% CI)
Highest BMI in lifetime (kg/m <sup>2</sup> ) <sup>c</sup>						
<25	159/336	1.0 (referent)	37/293	1.0 (referent)	31/281	1.0 (referent)
25 to 29.9	274/434	1.3 (1.0 to 1.7)	58/347	1.3 (0.8 to 2.0)	44/335	1.1 (0.6 to 1.8)
30 to 34.9	104/105	2.0 (1.4 to 2.8)	19/72	1.8 (1.0 to 3.5)	10/65	1.2 (0.5 to 2.6)
≥35.0	37/28	2.2 (1.3 to 3.8)	7/13	2.8 (1.0 to 8.1)	4/11	2.1 (0.6 to 7.6)
BMI at age 20 (kg/m <sup>2</sup> ) <sup>d</sup>						
<25.0	413/728	1.0 (referent)	81/588	1.0 (referent)	62/559	1.0 (referent)
≥25.0	64/51	2.4 (1.6 to 3.6)	17/33	3.6 (1.8 to 7.1)	12/33	3.0 (1.4 to 6.4)

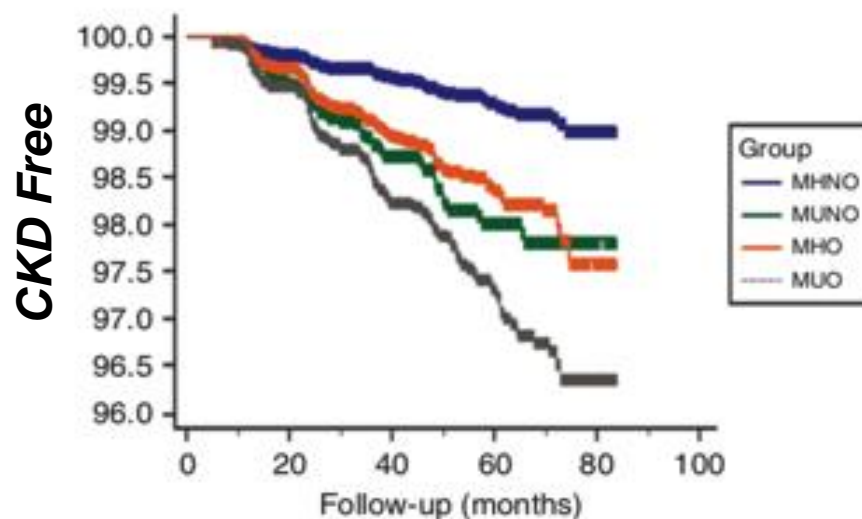
<sup>a</sup>Analyses are restricted to participants without self-reported diabetes and/or hypertension.

<sup>b</sup>Adjusted for age, gender, education, smoking, alcohol, and use of paracetamol and salicylates.

<sup>c</sup>Cut points in accordance with the WHO definition of overweight and obesity.

<sup>d</sup>Cut points in accordance with the WHO definition of overweight.

# CKD and Healthy Obese

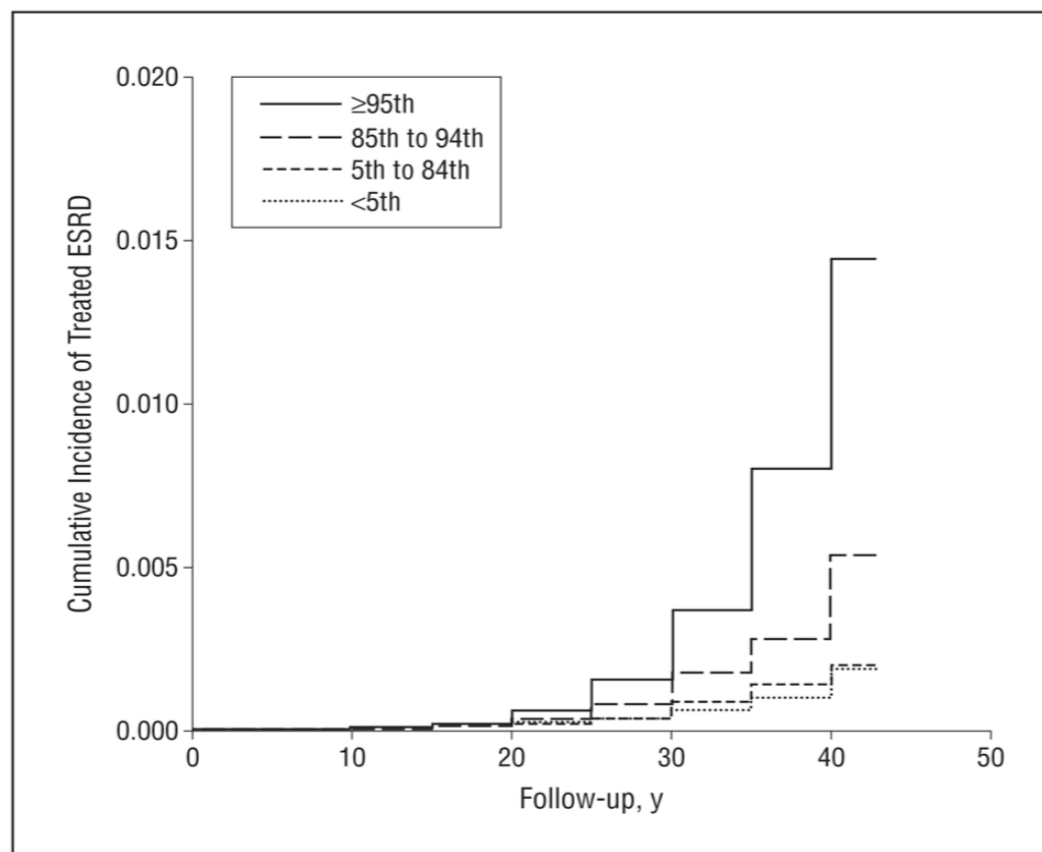


MHNO	20,329	15,473	9919	5517	111
MUNO	4835	3611	2345	1283	24
MHO	8587	6608	4340	2504	55
MUO	7443	5628	3558	1983	54

**Figure 2 | CKD-free survival determination by Kaplan-Meier analysis.** The median follow-up period was 38.7 months. Subjects were divided into four groups according to the baseline metabolic health and obesity status (log-rank test,  $P < 0.05$  for all comparisons except MUNO vs. MHO;  $P = 0.36$ ). The values under the chart indicate the number of participants at risk at 0 (baseline), 20, 40, 60, and 80 months of follow-up. CKD, chronic kidney disease; MHNO, metabolically healthy nonobese; MHO, metabolically healthy obese; MUNO, metabolically unhealthy nonobese; MUO, metabolically unhealthy obese.



# Adolescent BMI and Adult ESRD

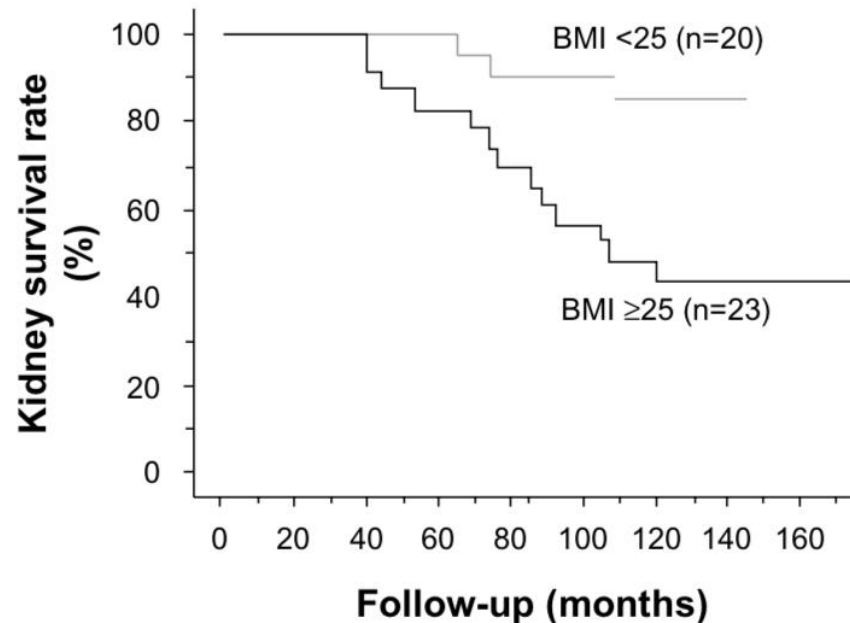


**Figure 1.**

Cumulative incidence of treated end-stage renal disease (ESRD) among participants according to body mass index percentile subgroup. Log-rank  $P < .001$ .

Vivante A. et. al. Arch Intern Med 2012; 172:1644–1650

# Obesity and IgA

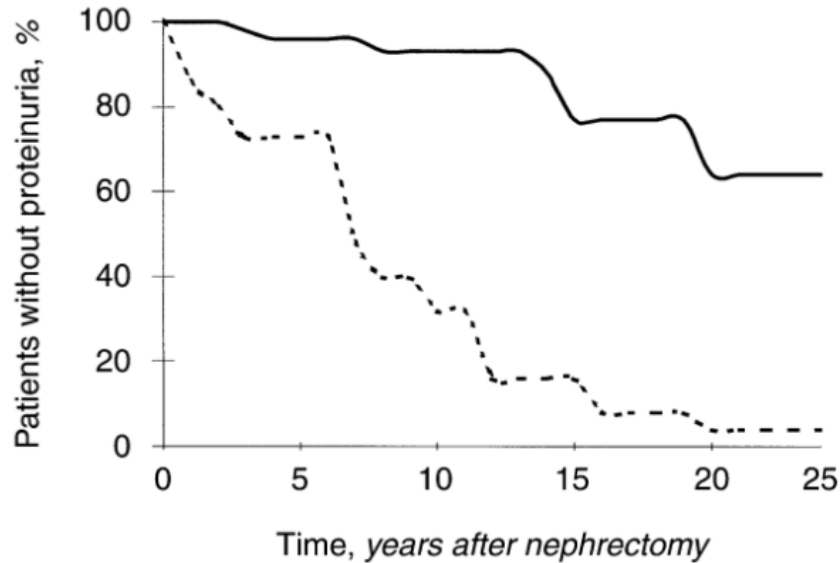


**Figure 2** Kidney survival rate of IgA nephropathy patients in the group with a BMI <25 kg/m<sup>2</sup> and the group with a BMI >25 kg/m<sup>2</sup>.

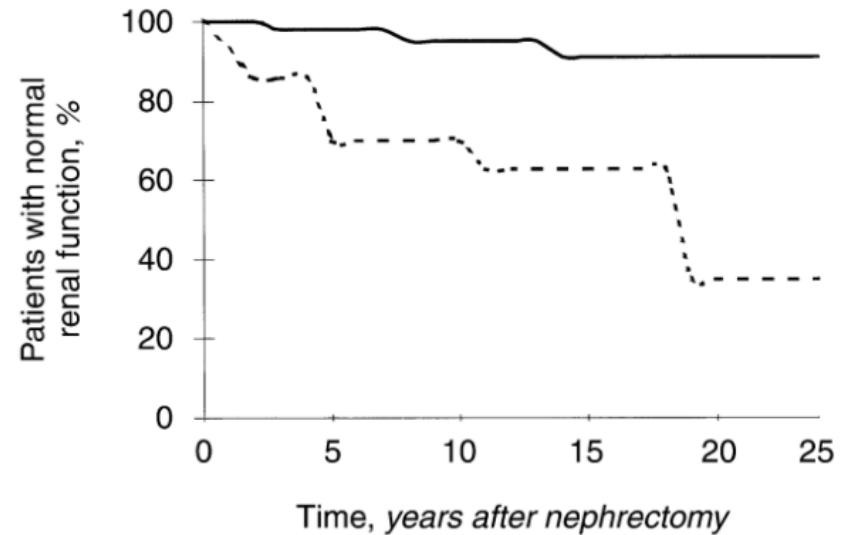
**Notes:** The 5 and 10 year kidney survival rates in the patients with BMI <25 kg/m<sup>2</sup> were 100% and 85%, respectively, compared to 82.6% and 43.5%, respectively, in the group with BMI >25 kg/m<sup>2</sup>. Copyright © 2012. Adapted from Kataoka H, Ohara M, Shibui K, et al. Overweight and obesity accelerate the progression of IgA nephropathy: prognostic utility of a combination of BMI and histopathological parameters. *Clin Exp Nephrol*. 2012;16(5):706–712.<sup>20</sup>

**Abbreviations:** BMI, body mass index; IgA, immunoglobulin A.

# Obesity and Unilateral Nephrectomy

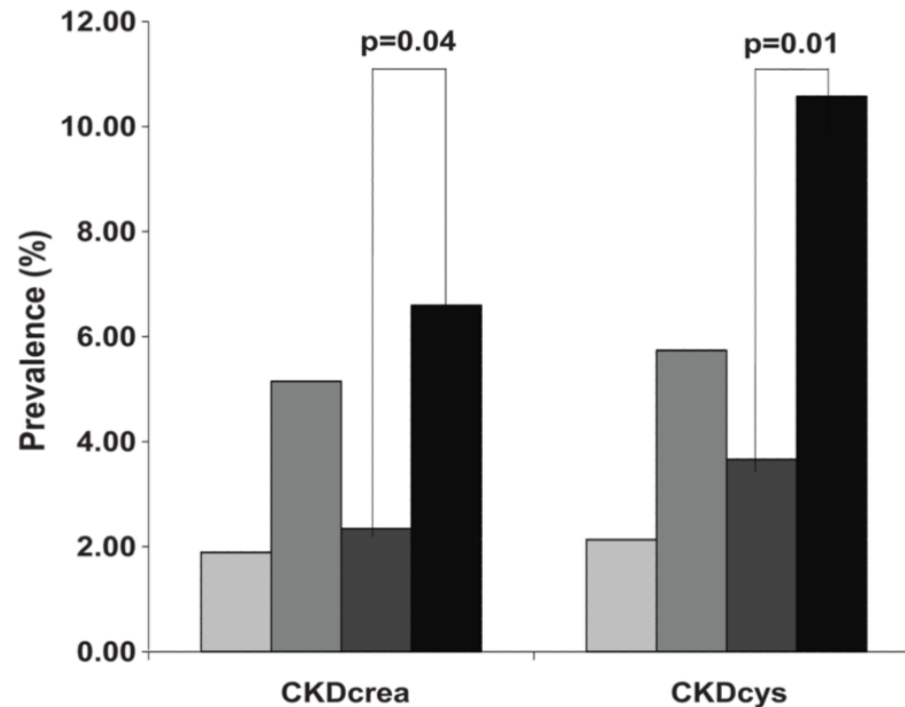


**Fig. 3.** Probability of negative proteinuria in obese (dashed line) and nonobese (solid line) patients (log-rank test,  $P < 0.001$ ).



**Fig. 4.** Probability of normal renal function in obese (dashed line) and nonobese (solid line) patients (log-rank test,  $P < 0.001$ ).

# Renal Sinus Fat “Fatty Kidneys” and CKD



**Figure 1. Prevalence of Chronic Kidney Disease (CKD) by Fatty Kidney and Abdominal Visceral Adipose Tissue (VAT) Distribution Patterns**

CKD<sub>cys</sub> is defined as  $eGFR < 60 \text{ mL/min/1.73m}^2$ , based on the Cystatin-C only CKD-EPI equation. CKD<sub>crea</sub> is defined as  $eGFR < 60 \text{ mL/min/1.73m}^2$ , based on the modified MDRD Study Equation. ■ Not fatty kidney and normal VAT (Group 1); ■ Fatty kidney and Normal VAT (Group 2); ■ Not fatty kidney and high VAT (Group 3); ■ Fatty kidney and high VAT (Group 4). For comparison, CKD<sub>cys</sub> and CKD<sub>crea</sub> status at the 7<sup>th</sup> Offspring exam cycle are presented. P-values are adjusted for age and sex. CKD<sub>crea</sub> available in 2943 participants (Group 1 N=1437; Group 2 N=236; Group 3 N=605; Group 4 N=665). CKD<sub>cys</sub> available in 1206 participants with cystatin-C measures (Group 1 N=375; Group 2 N=122; Group 3 N=273; Group 4 N=436).

# Renal Lipotoxicity

- Lipids may cause renal mesangial and epithelial cell injury and may promote renal disease progression

Moorhead JF et. al. *Lancet* 2: 1309–1311, 1982

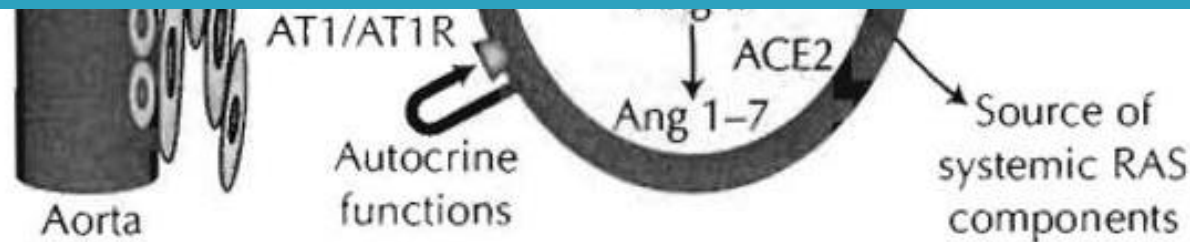
Ruan XZ et al. *Biochem Soc Trans* 32: 88–91, 2004



# Adipocyte RAAS

**Adipose tissue produces angiotensinogen**

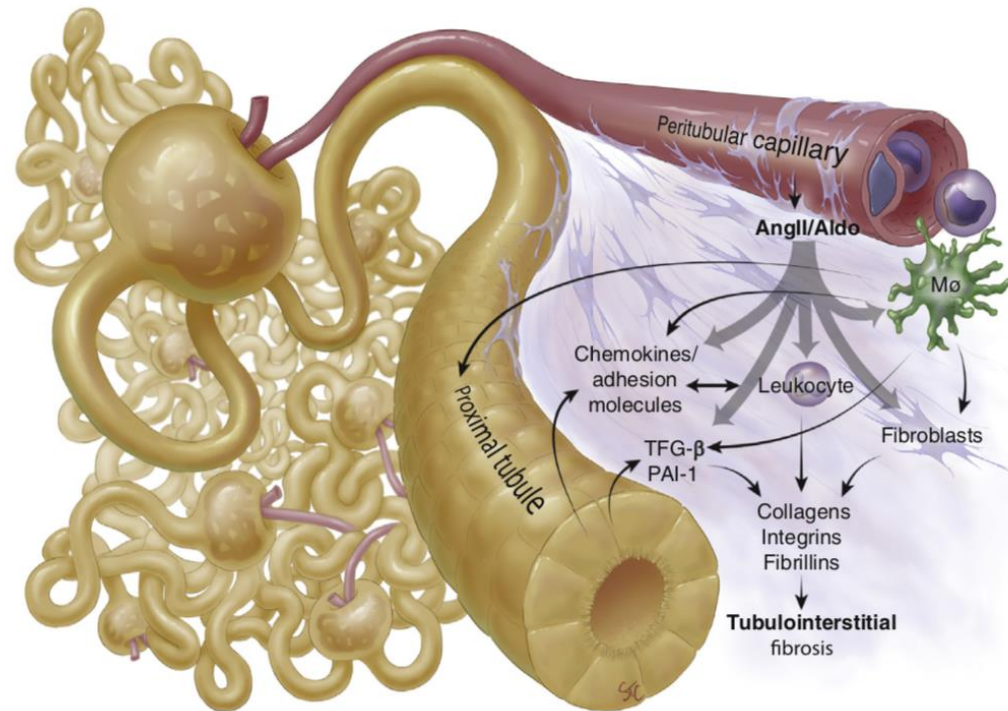
**Adipocytes express AT1 and AT2 receptors**



Cassis LA. Curr Hypertens Rep. 2008 April; 10(2): 93–98



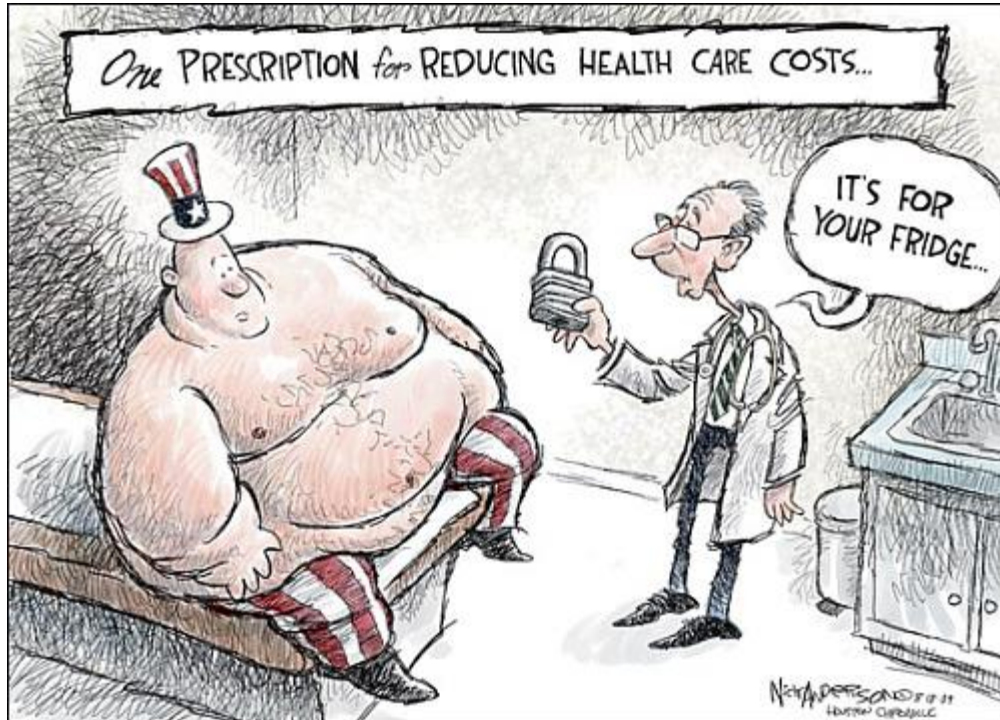
# RAS and Fibrosis



**Figure 2 | The renin angiotensin aldosterone system (RAAS) in tubulointerstitial fibrosis.** Angiotensin (Ang) II and aldosterone (Aldo) induce profibrotic instigators in the endothelium as well as in the proximal tubule that promote tumor growth factor  $\beta$  (TGF- $\beta$ ) and plasminogen activator inhibitor-1 (PAI-1) secretion and stimulate endothelial cell stiffness, vascular fibrosis, and extracellular matrix deposition in the kidney. Ang II and Aldo have also been shown to elicit an immune response in the kidney through monocyte chemotaxis, macrophage (M $\phi$ ) polarization, and various chemokines that contribute to endothelial dysfunction and tubulointerstitial fibrosis.



# Treatment



Magic Pills





# ORG: Effect of Weight Loss

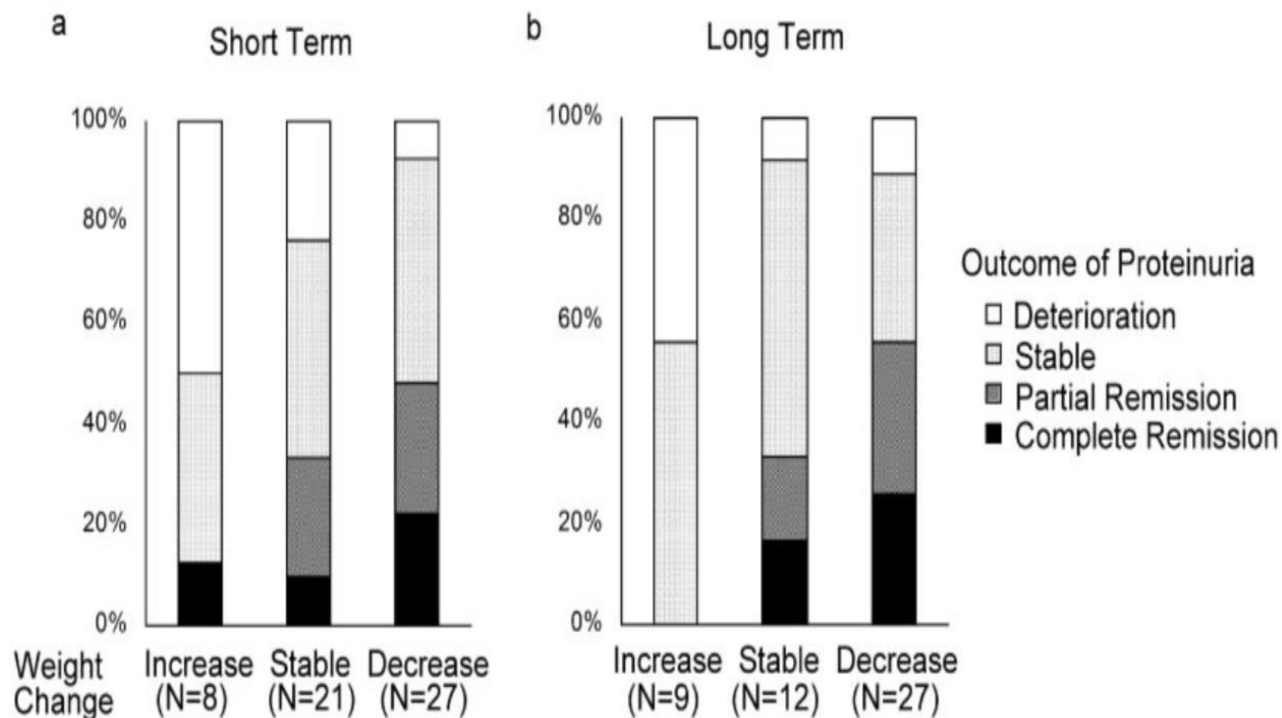
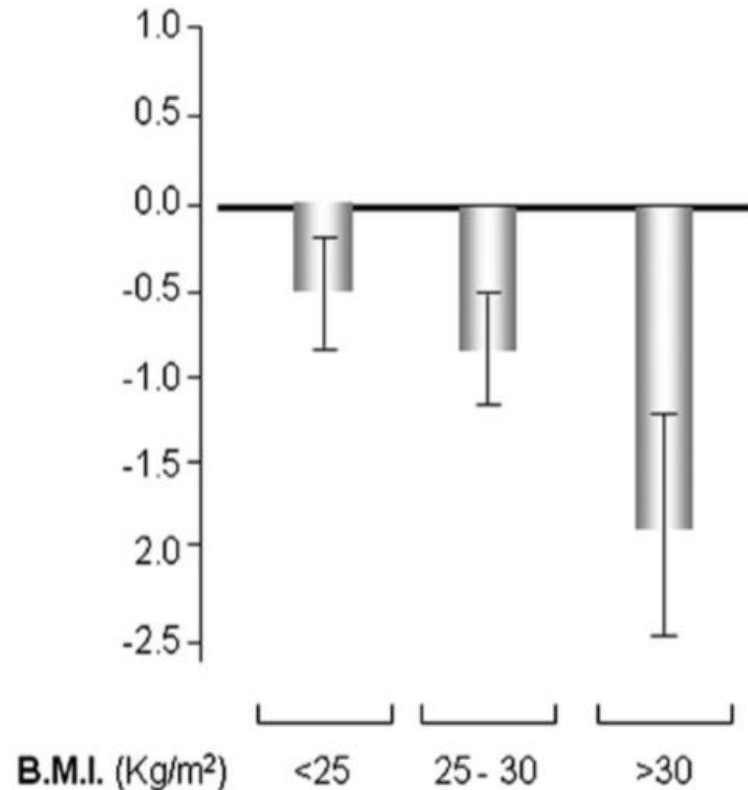


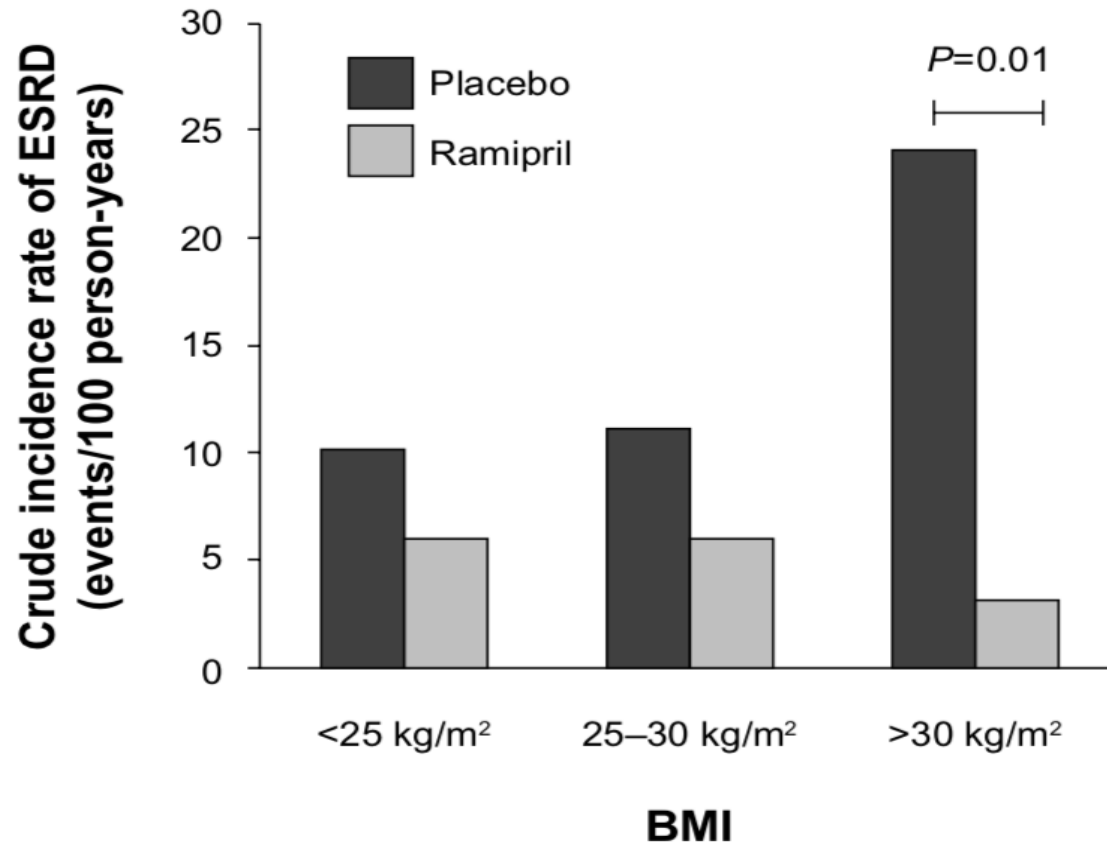
Figure 1. Relationship between changes in body weight and outcome of proteinuria at the (a) 6th month (short term) and (b) 24th month (long term).

# Ramipril and Proteinuria in Obese

Differences in Urinary Protein Excretion  
(Ramipril versus Placebo)



# Ramipril and ESRD in Obese



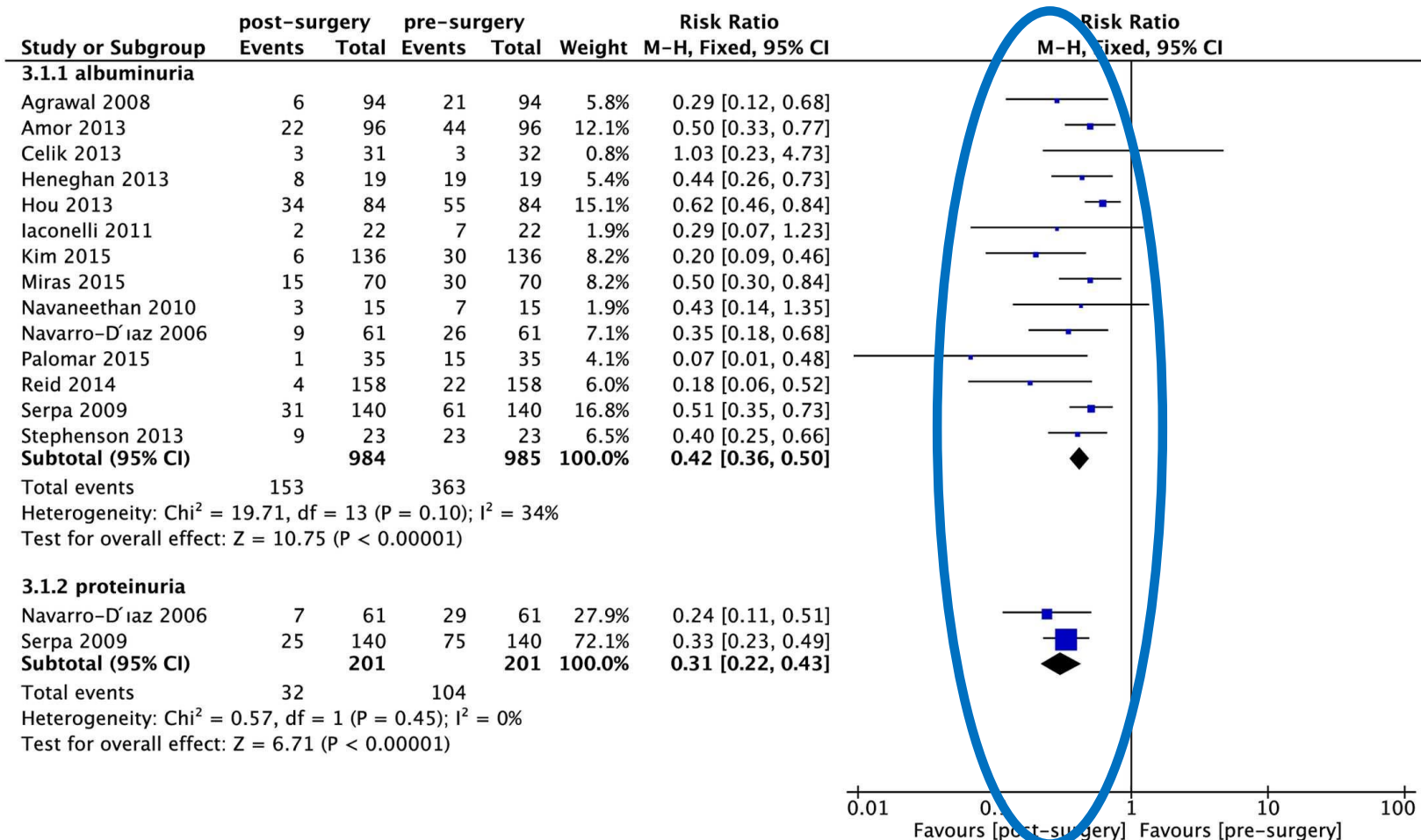
**Figure 6** The incidence of ESRD for obese, normal, and overweight patients and the effect of ramipril treatment.

# Treatment: Bariatric Surgery

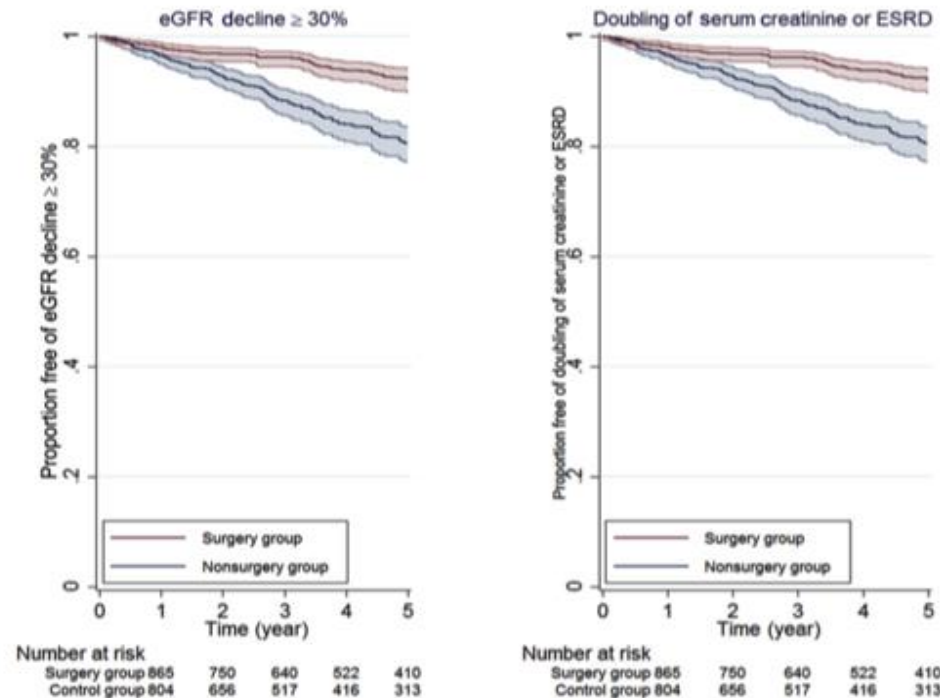
- Increasing use in adolescents
- Safe



# Bariatric Surgery and Proteinuria

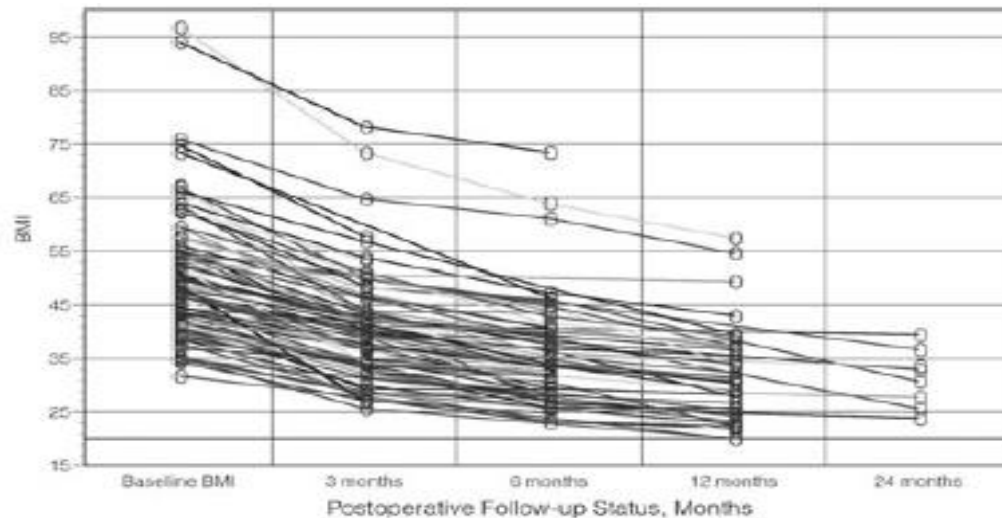


# Bariatric Surgery and Kidney Outcomes



**Figure 4.** Kaplan–Meier curves estimating time to kidney outcomes by surgery group ( $n = 985$ ) and control group ( $n = 985$ ). Figure from Chang *et al.*<sup>48</sup> Estimated glomerular filtration (eGFR) decline  $\geq 30\%$  outcome was defined as having a follow-up outpatient eGFR  $\geq 30\%$  lower than the baseline eGFR value. End-stage renal disease (ESRD) was defined as eGFR  $< 15$  ml/min/1.73 m<sup>2</sup> or treated ESRD per US Renal Data System Registry. Shaded areas represent 95% confidence interval bounds.

# Treatment: Bariatric Surgery



108 Children  
5 – 21 y/o  
Laparoscopic gastrectomy

**TABLE 4. Resolution of Comorbidities**

Condition	Patients With Data Available <sup>†</sup>	Resolved, n (%)
Symptoms of obstructive sleep apnea	22	20 (90.9)
Prediabetes	11	11 (100.0)
Diabetes	16	15 (93.8)
Prehypertension	18	15 (83.3)
Hypertension	36	27 (75.0)
Dyslipidemia	30	21 (70.0)



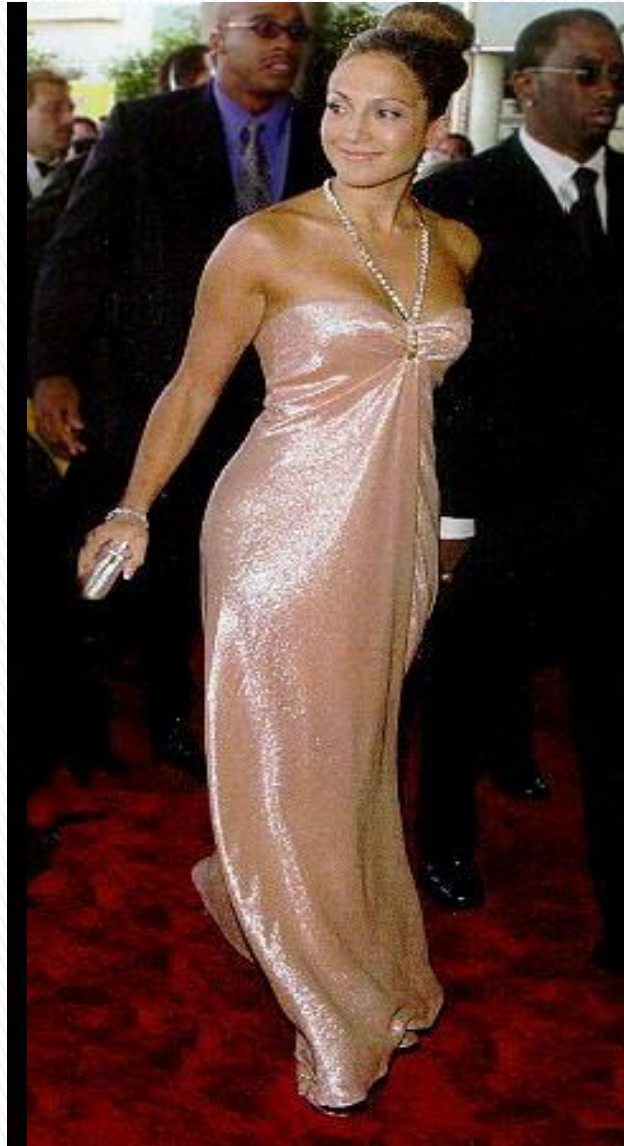
# Strategies to Delay Progression

- RAAS inhibition
- Weight loss
  - Diet and Exercise
  - Bariatric surgery
- Novel strategies involve administration of small molecules that specifically modulate deleterious pathways of fatty acid and cholesterol metabolism





# Thanks



# Questions?