15th Budapest Nephrology School

August 26-31, 2008
Semmelweis University, Budapest, Hungary

Obesity

(Obesity and the kidney)

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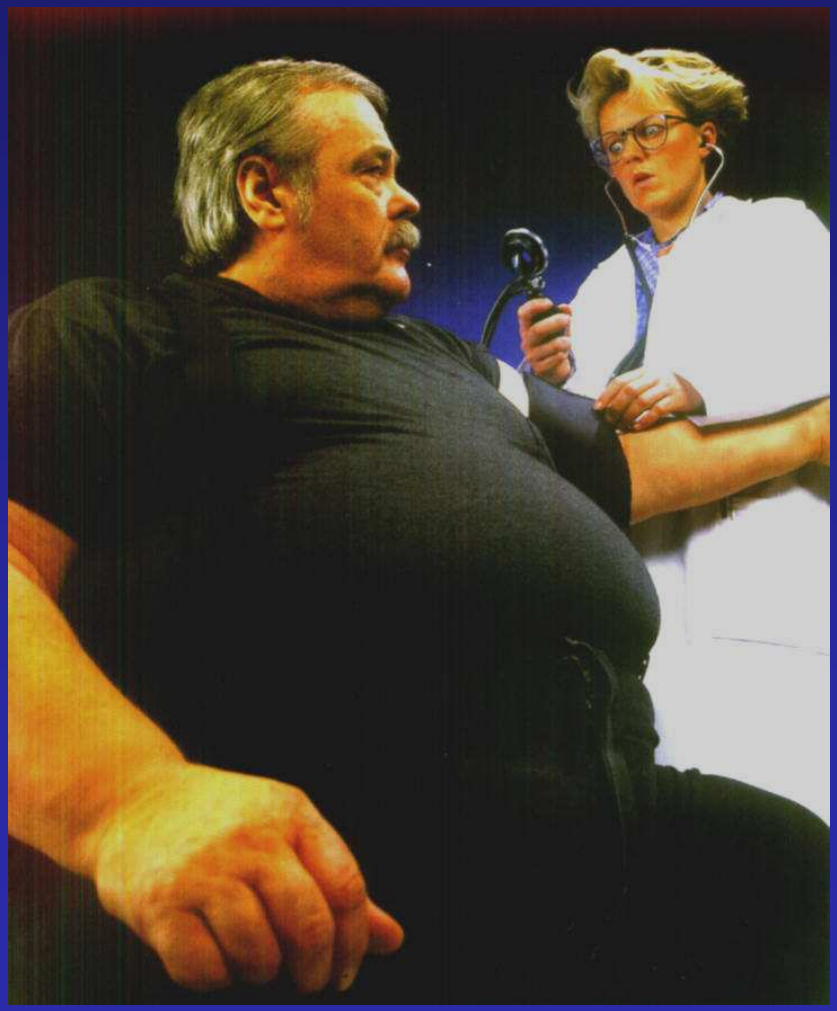
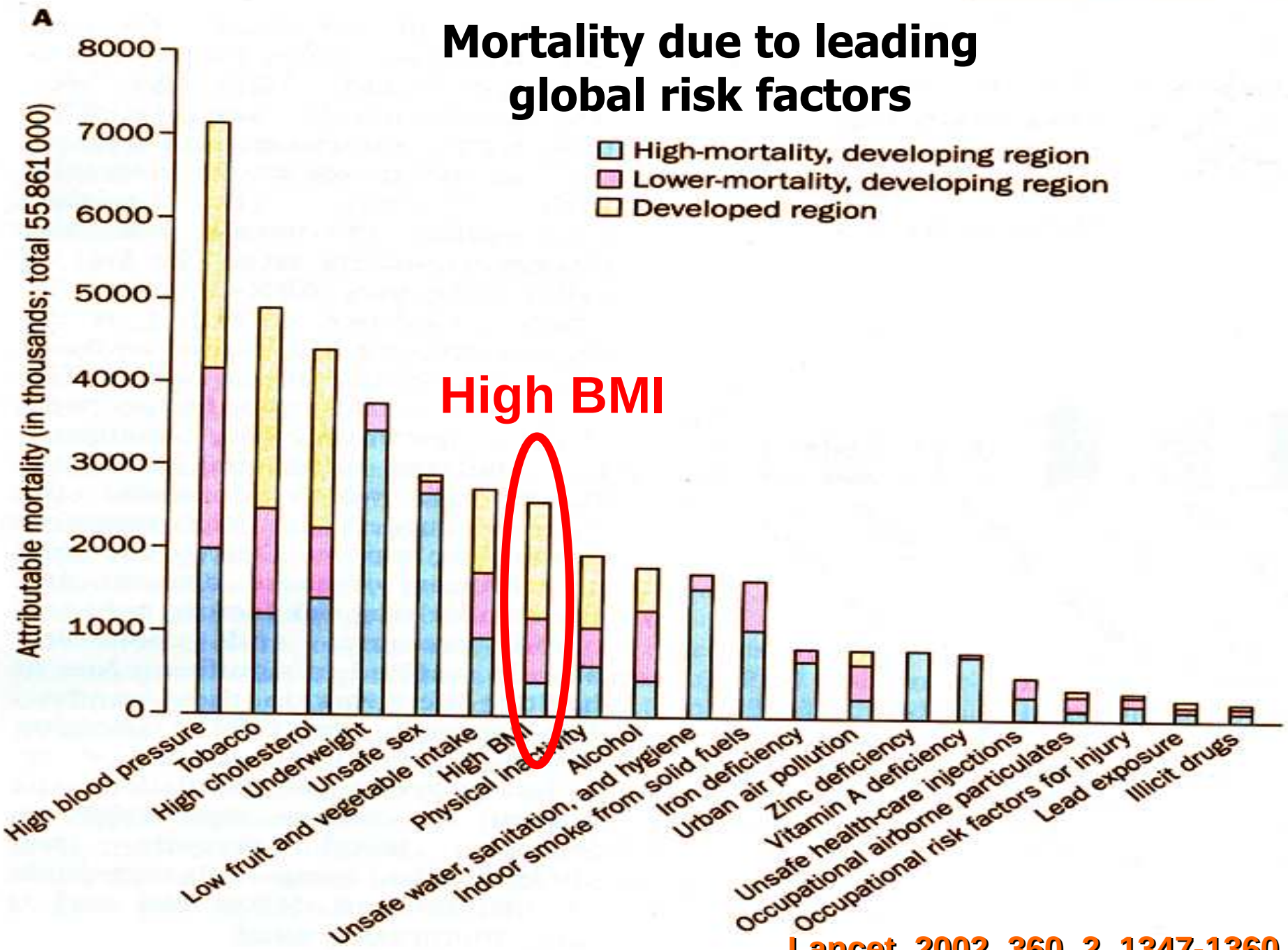
Dept. Nephrology, Endocrinology and Metabolic Diseases
Medical University of Silesia, Katowice, Poland

awiecek@spskm.katowice.pl

Obesity- the public health problem in Western Countries



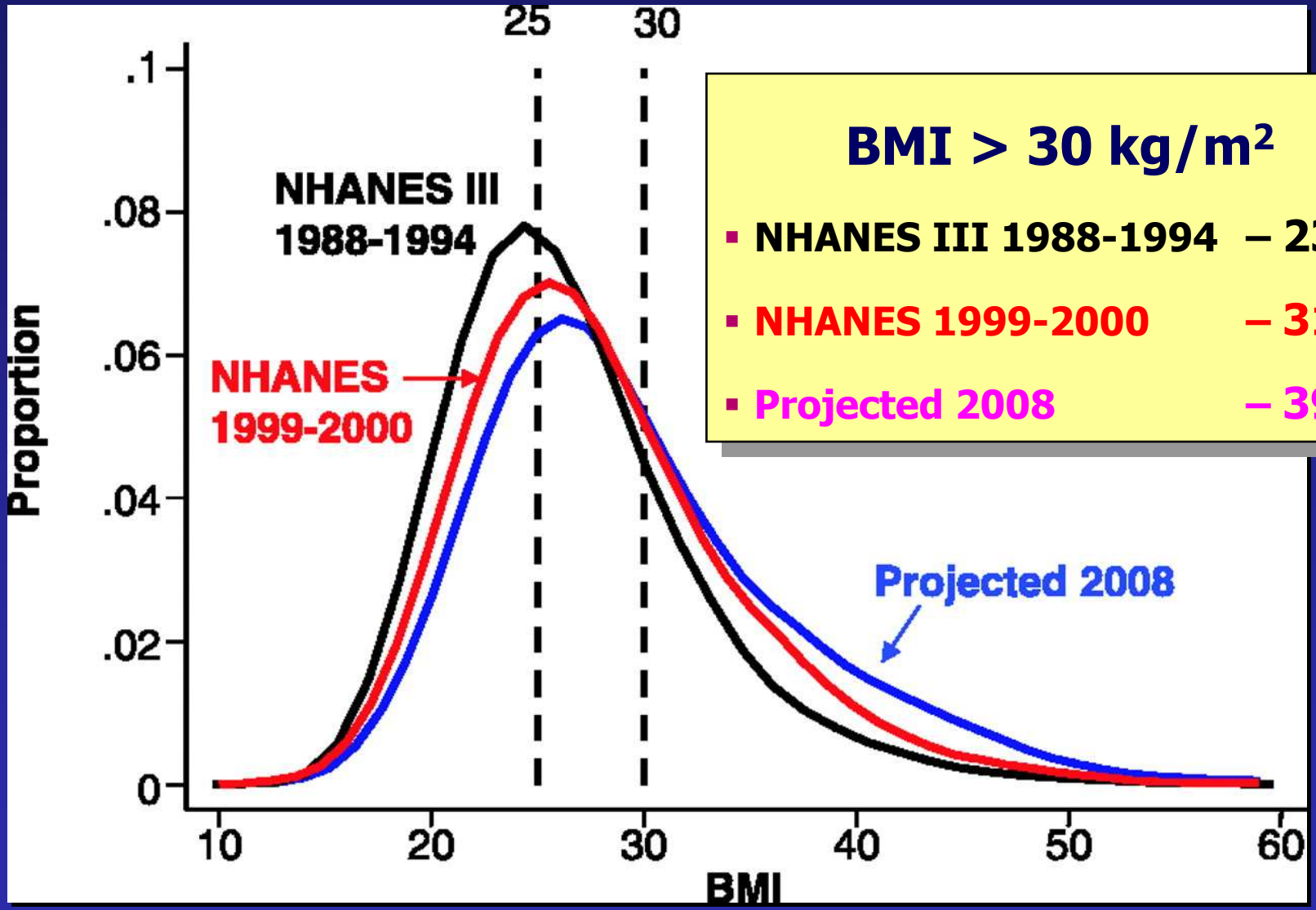
Mortality due to leading global risk factors



Lancet, 2002, 360, 2, 1347-1360

BMI trends among U.S. adults 1988-2008

National Health and Nutrition Examination Survey (USA)



BMI > 30 kg/m²

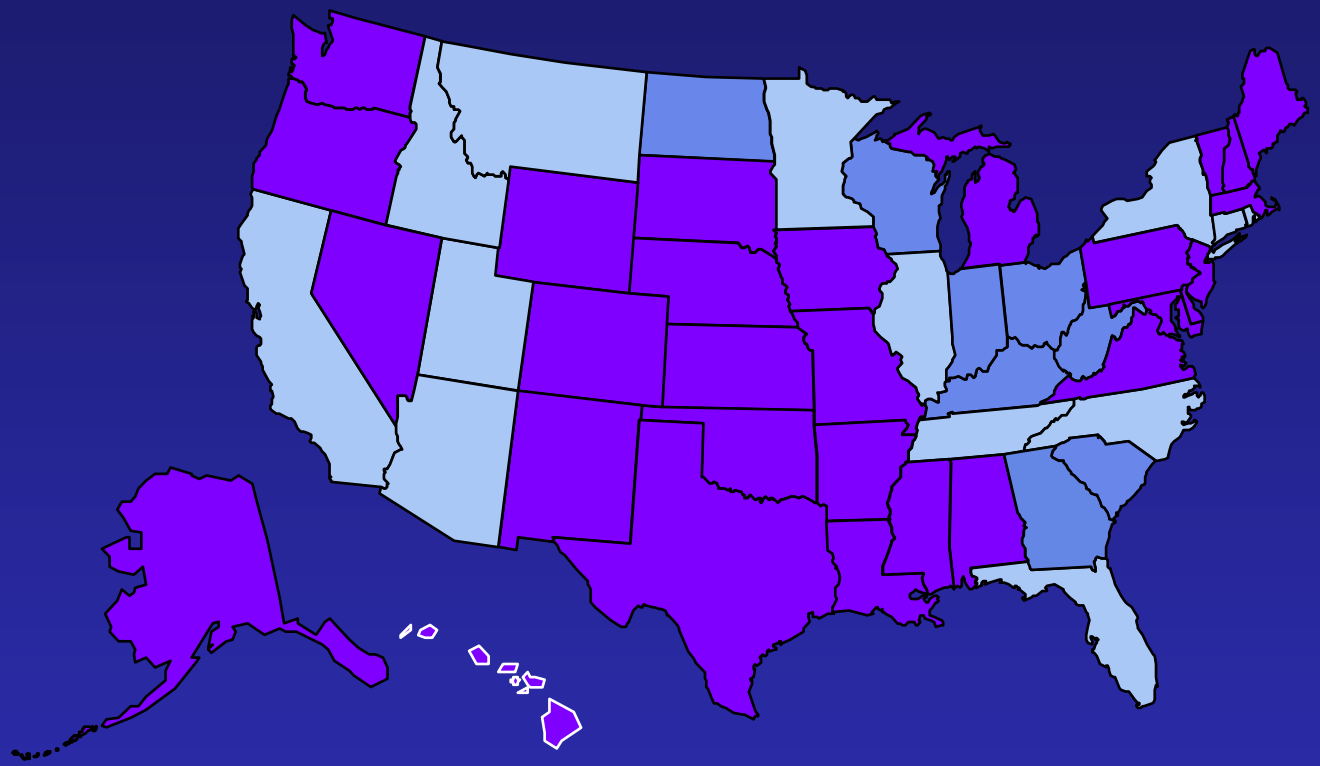
- NHANES III 1988-1994 – 23%
- NHANES 1999-2000 – 31%
- Projected 2008 – 39%

Hill J.O. et al., Science, 2003, 299, 853-855

Obesity Trends Among U.S. Adults

Behavioral Risk Factors Surveillance System - 1985

BMI ≥30

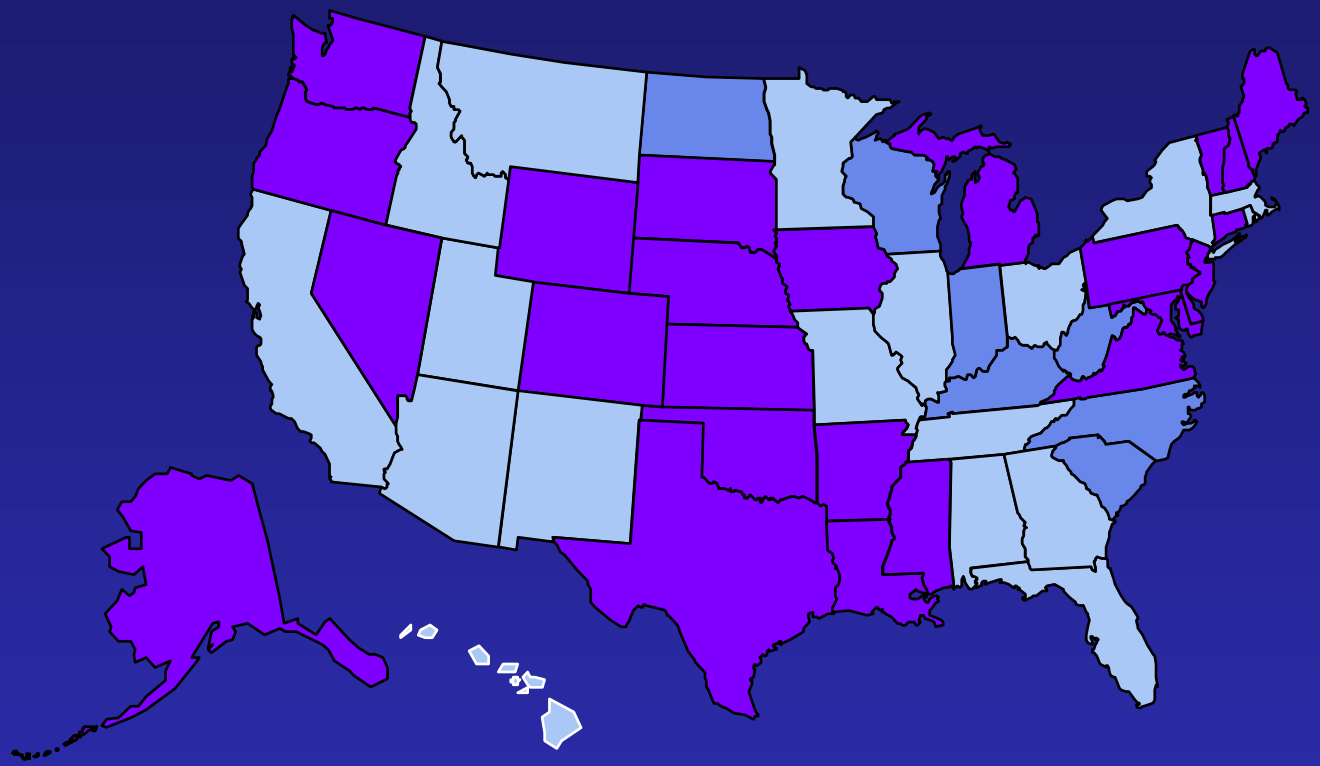


No Data | <10% | 10%–14%

U.S Obesity Trends 1985-2006, CDC (www.cdc.gov)

Obesity Trends Among U.S. Adults
BRFSS, 1986

BMI ≥30



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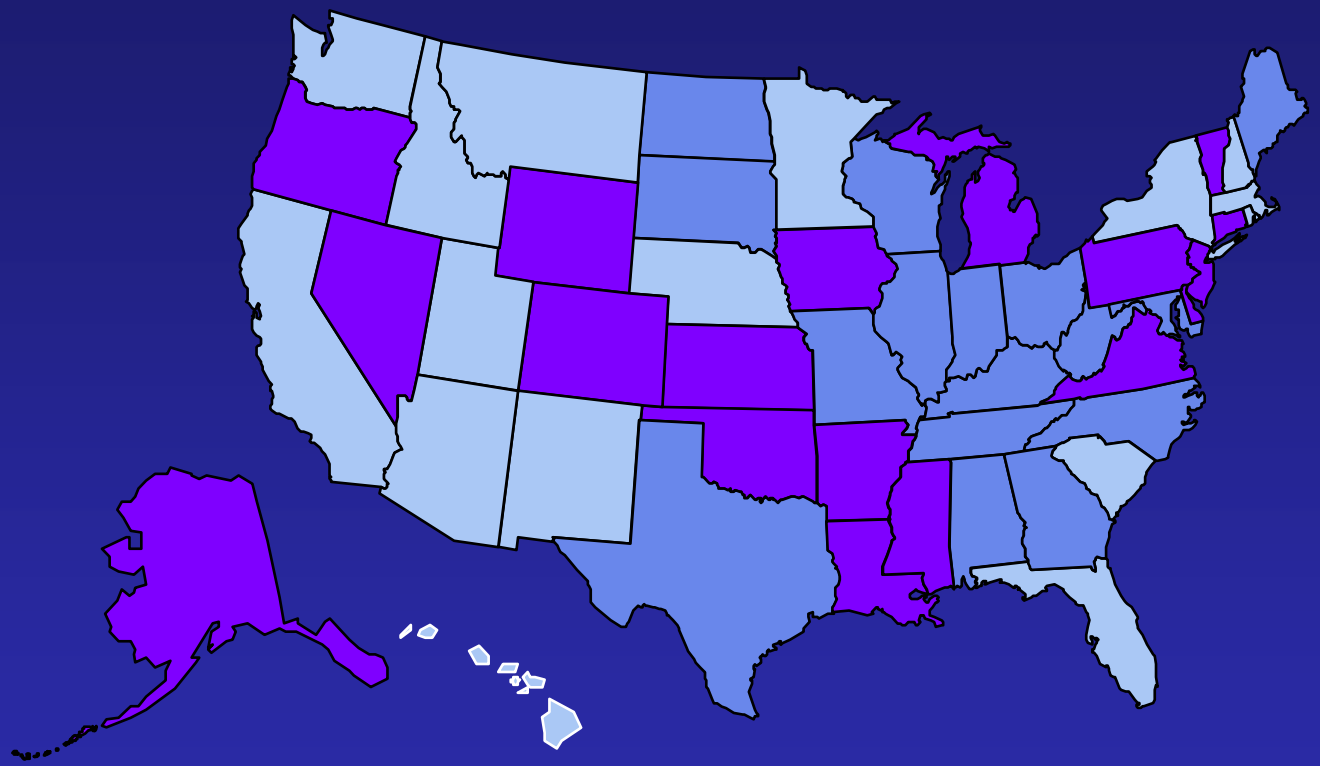
Obesity Trends Among U.S. Adults
BRFSS, 1987

BMI ≥30



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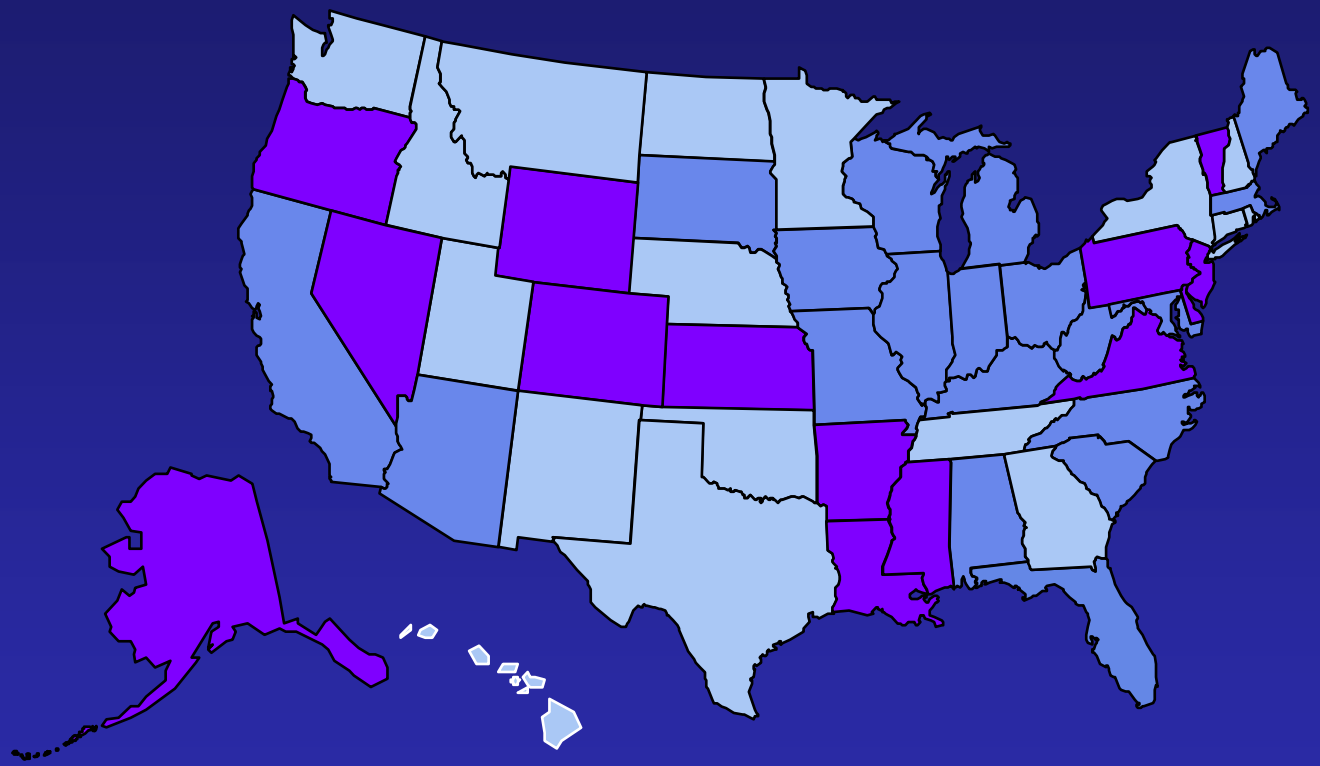
U.S Obesity Trends 1985-2006, CDC (www.cdc.gov)

Obesity Trends Among U.S. Adults
BRFSS, 1988

BMI ≥30

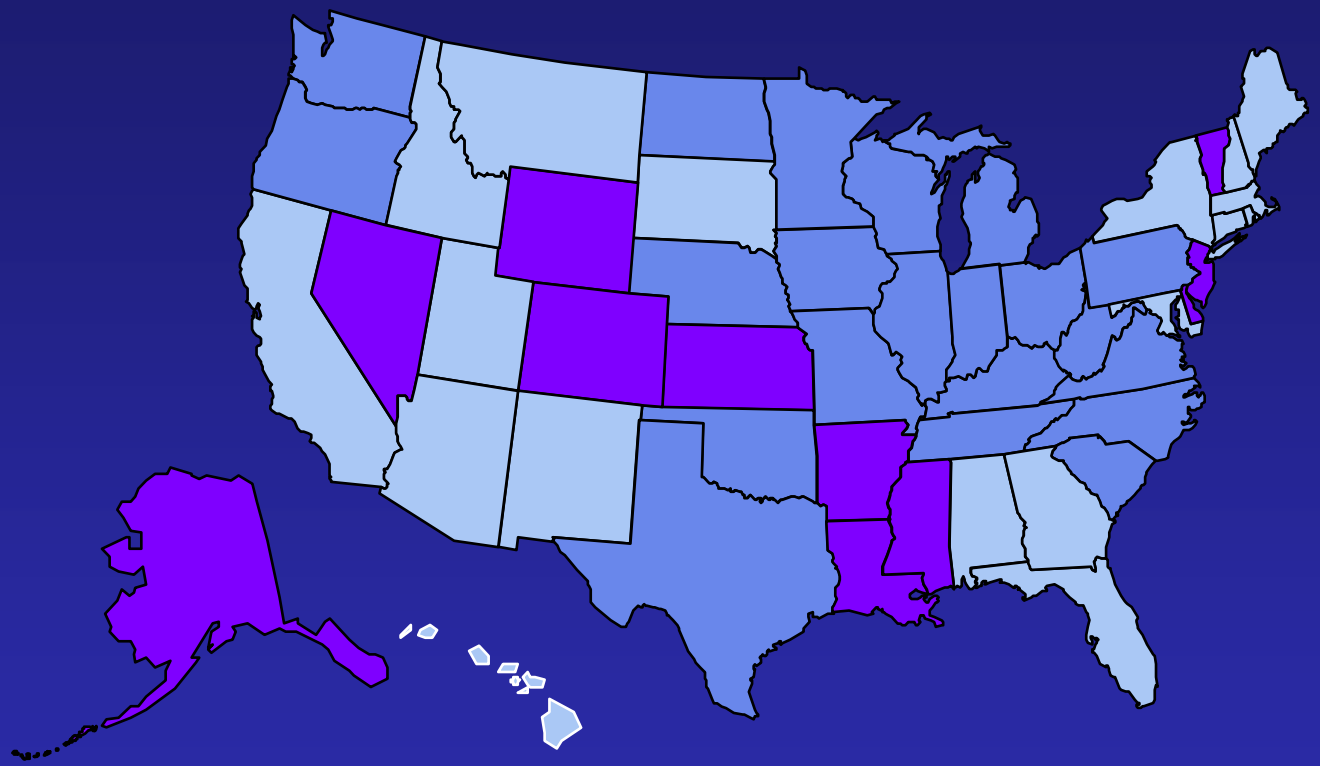


No Data | <10% | 10%–14%

U.S Obesity Trends 1985-2006, CDC (www.cdc.gov)

Obesity Trends Among U.S. Adults
BRFSS, 1989

BMI ≥30

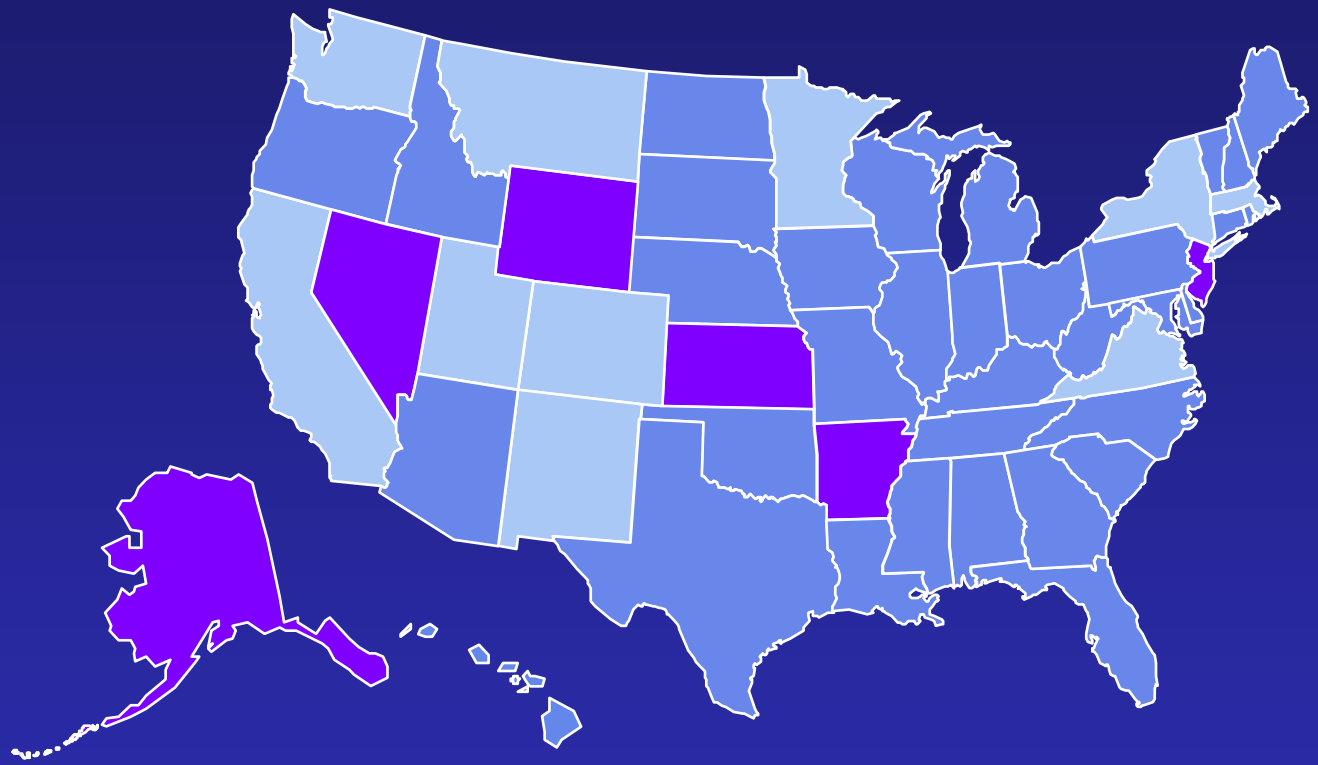


No Data | <10% | 10%–14%

U.S Obesity Trends 1985-2006, CDC (www.cdc.gov)

Obesity Trends Among U.S. Adults
BRFSS, 1990

BMI ≥30

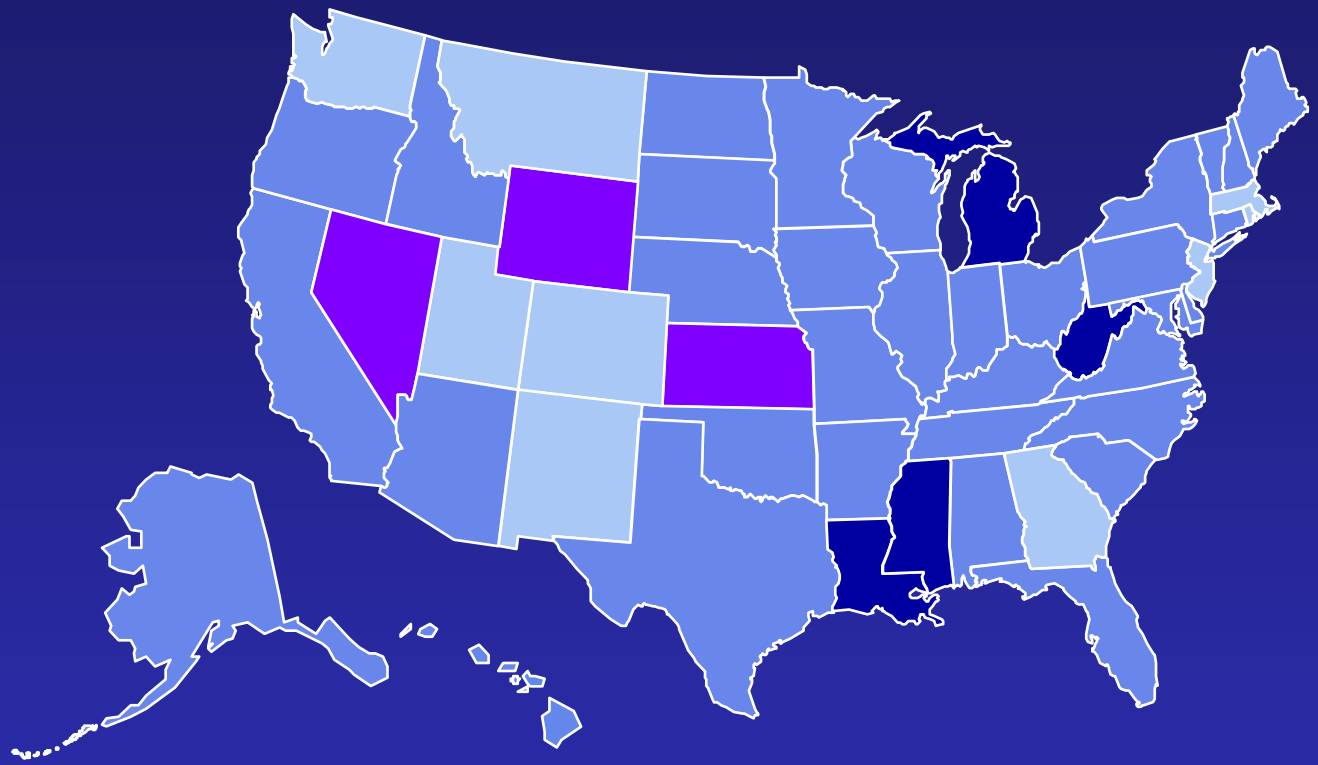


No Data | <10% | 10%–14%

U.S Obesity Trends 1985-2006, CDC (www.cdc.gov)

Obesity Trends Among U.S. Adults
BRFSS, 1991

BMI ≥30

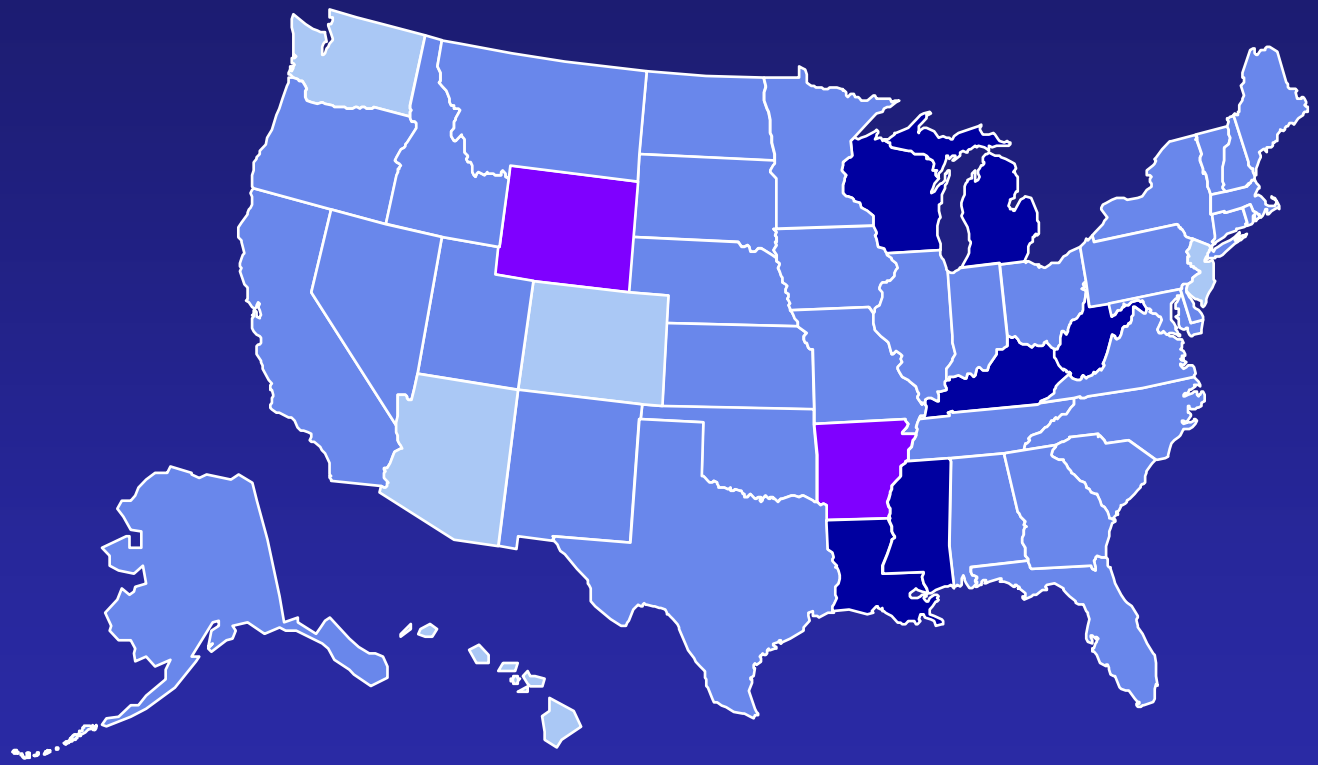


No Data | <10% | 10%–14% | 15%–19%

U.S Obesity Trends 1985-2006, CDC (www.cdc.gov)

Obesity Trends Among U.S. Adults
BRFSS, 1992

BMI ≥30

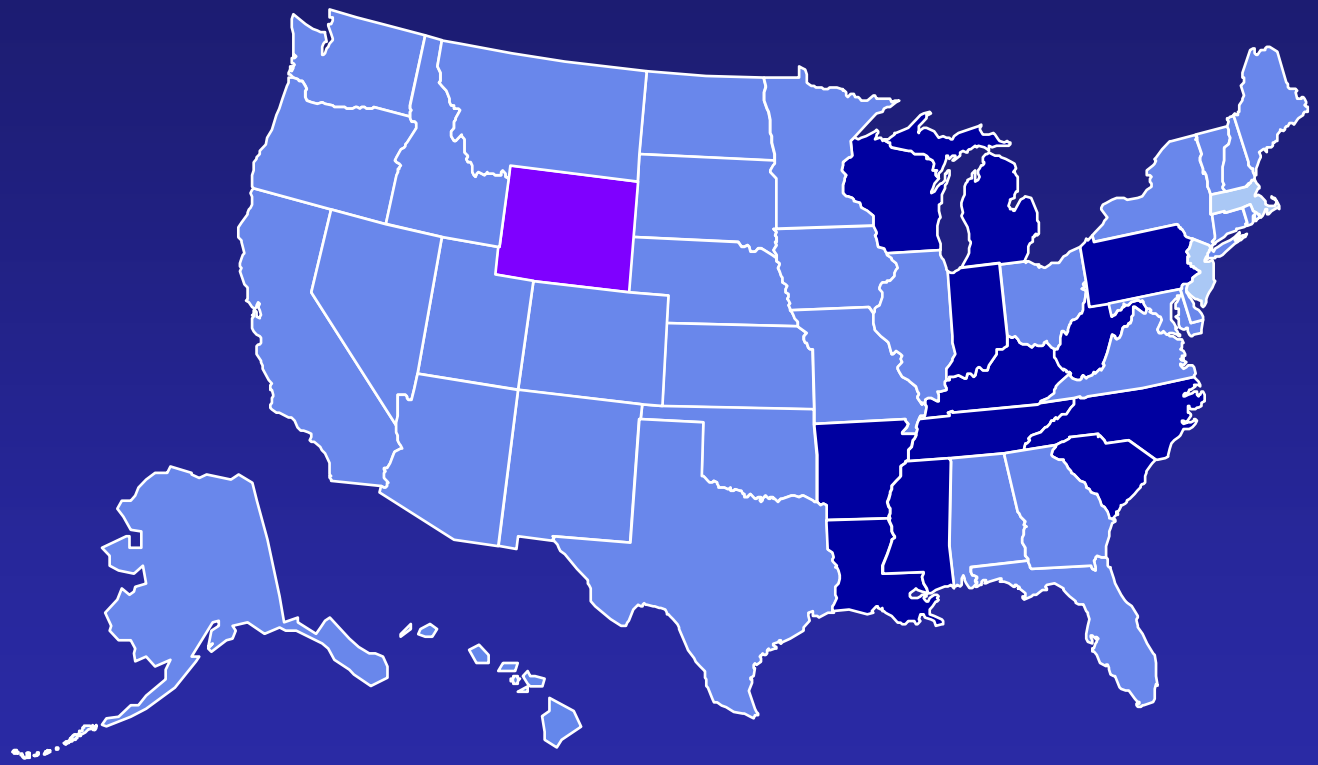


No Data | <10% | 10%–14% | 15%–19%

U.S Obesity Trends 1985-2006, CDC (www.cdc.gov)

Obesity Trends Among U.S. Adults
BRFSS, 1993

BMI ≥30

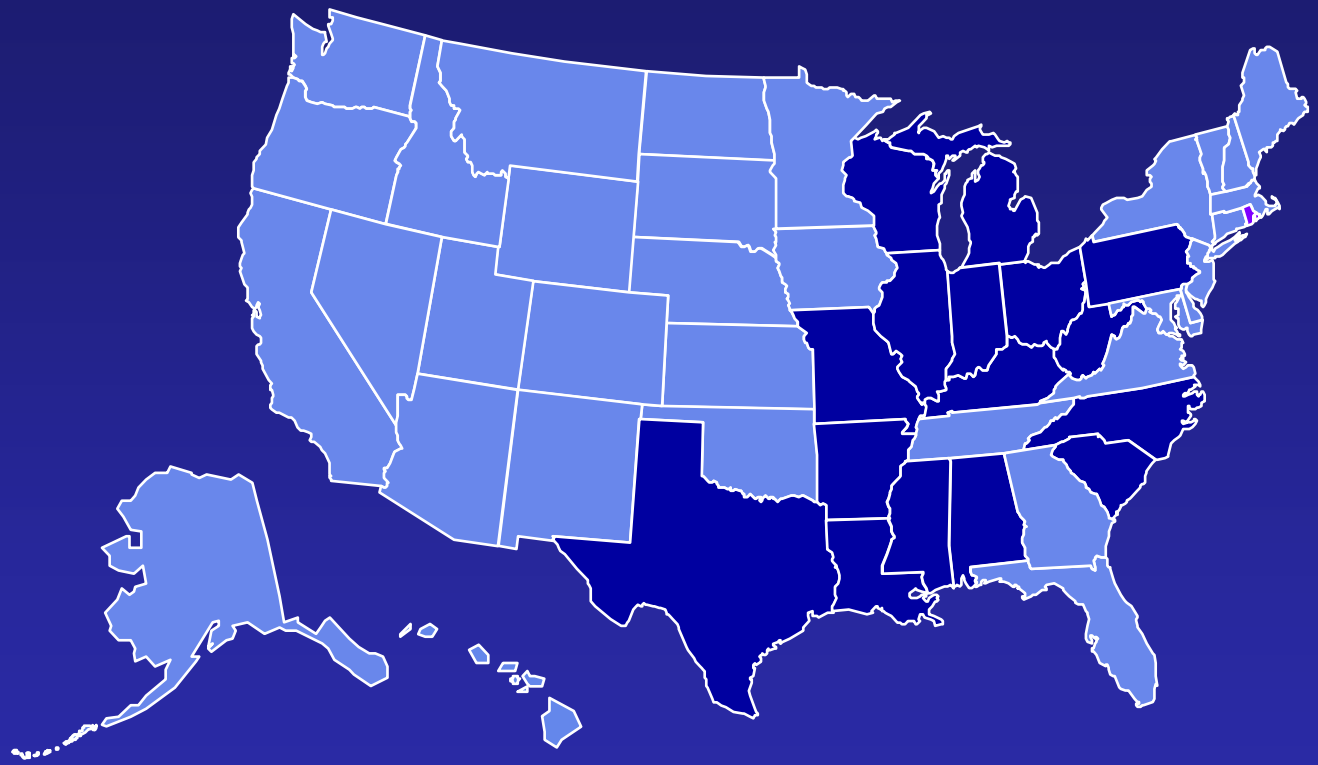


No Data | <10% | 10%–14% | 15%–19%

U.S Obesity Trends 1985-2006, CDC (www.cdc.gov)

Obesity Trends Among U.S. Adults
BRFSS, 1994

BMI ≥30

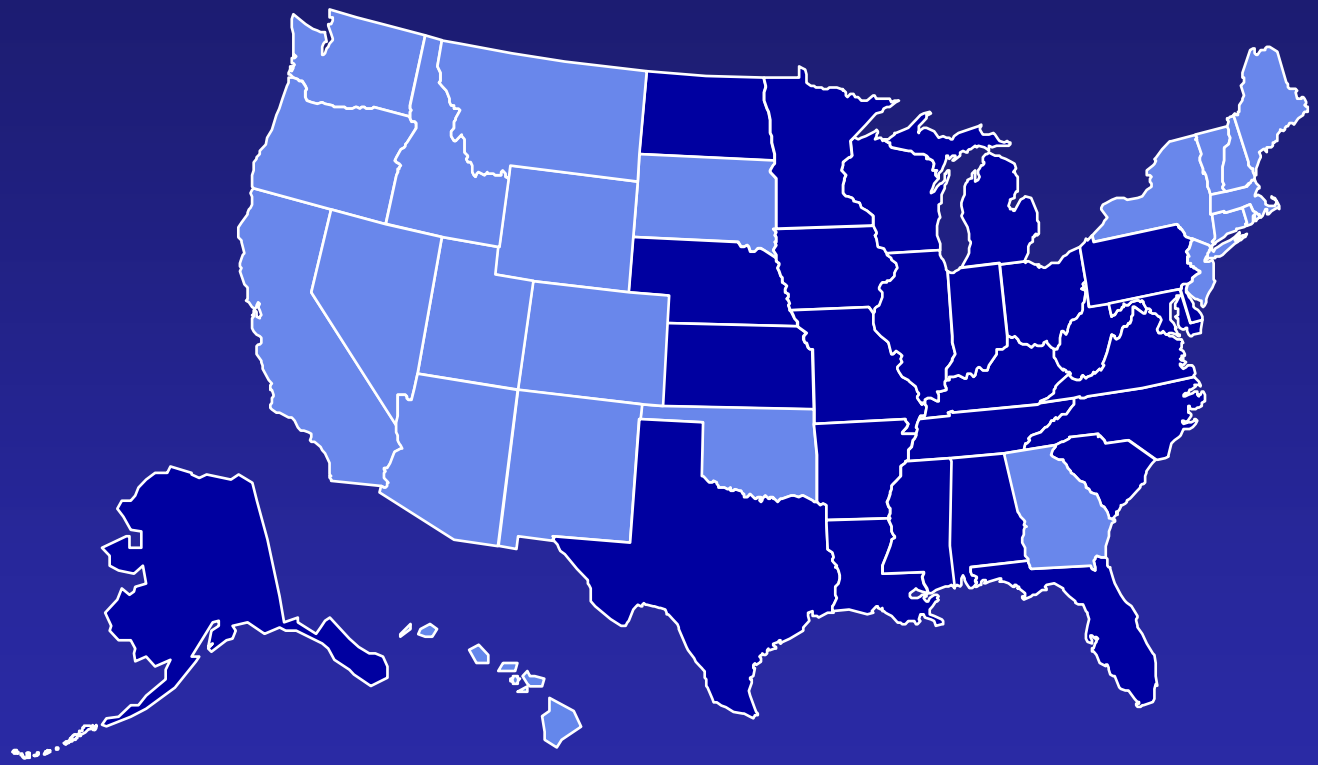


No Data | <10% | 10%–14% | 15%–19%

U.S Obesity Trends 1985-2006, CDC (www.cdc.gov)

Obesity Trends Among U.S. Adults
BRFSS, 1995

BMI ≥30

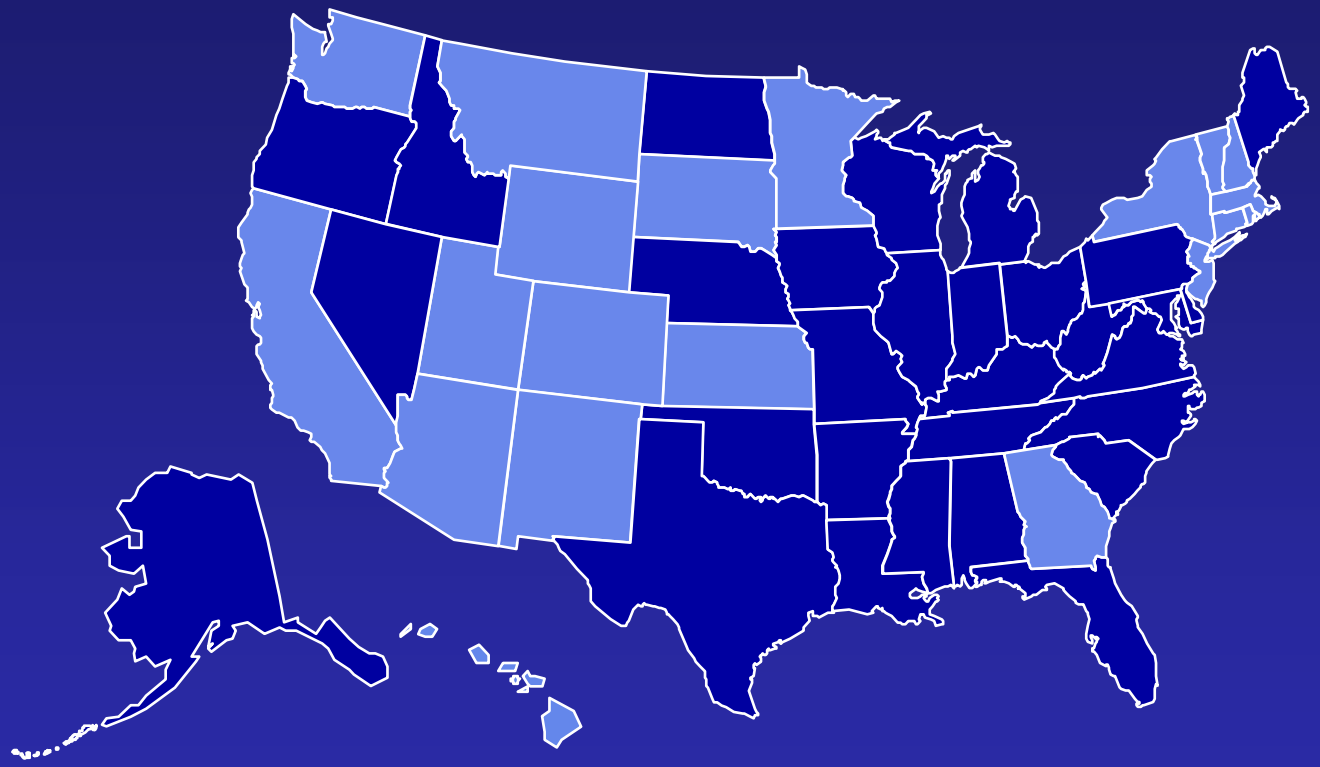


No Data | <10% | 10%–14% | 15%–19%

U.S Obesity Trends 1985-2006, CDC (www.cdc.gov)

Obesity Trends Among U.S. Adults
BRFSS, 1996

BMI ≥30

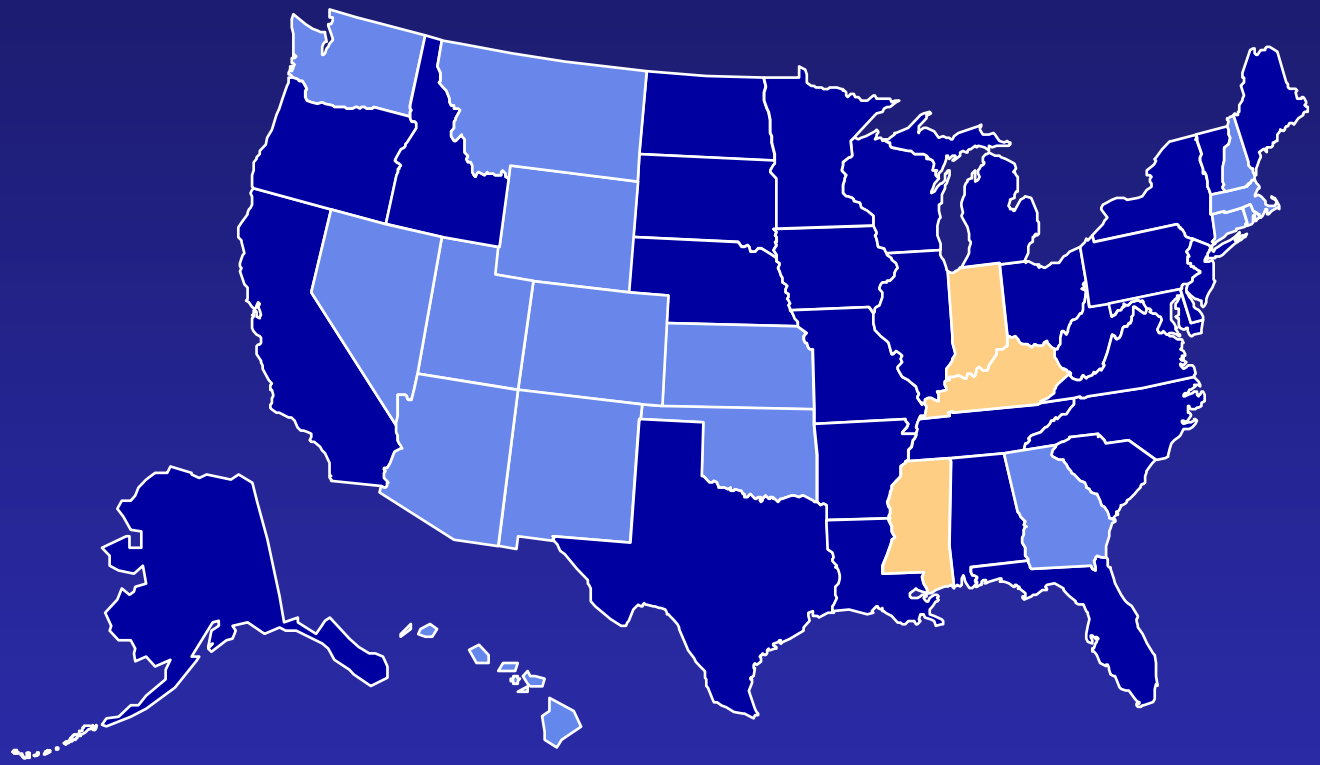


No Data | <10% | 10%–14% | 15%–19%

U.S Obesity Trends 1985-2006, CDC (www.cdc.gov)

Obesity Trends Among U.S. Adults
BRFSS, 1997

BMI ≥30

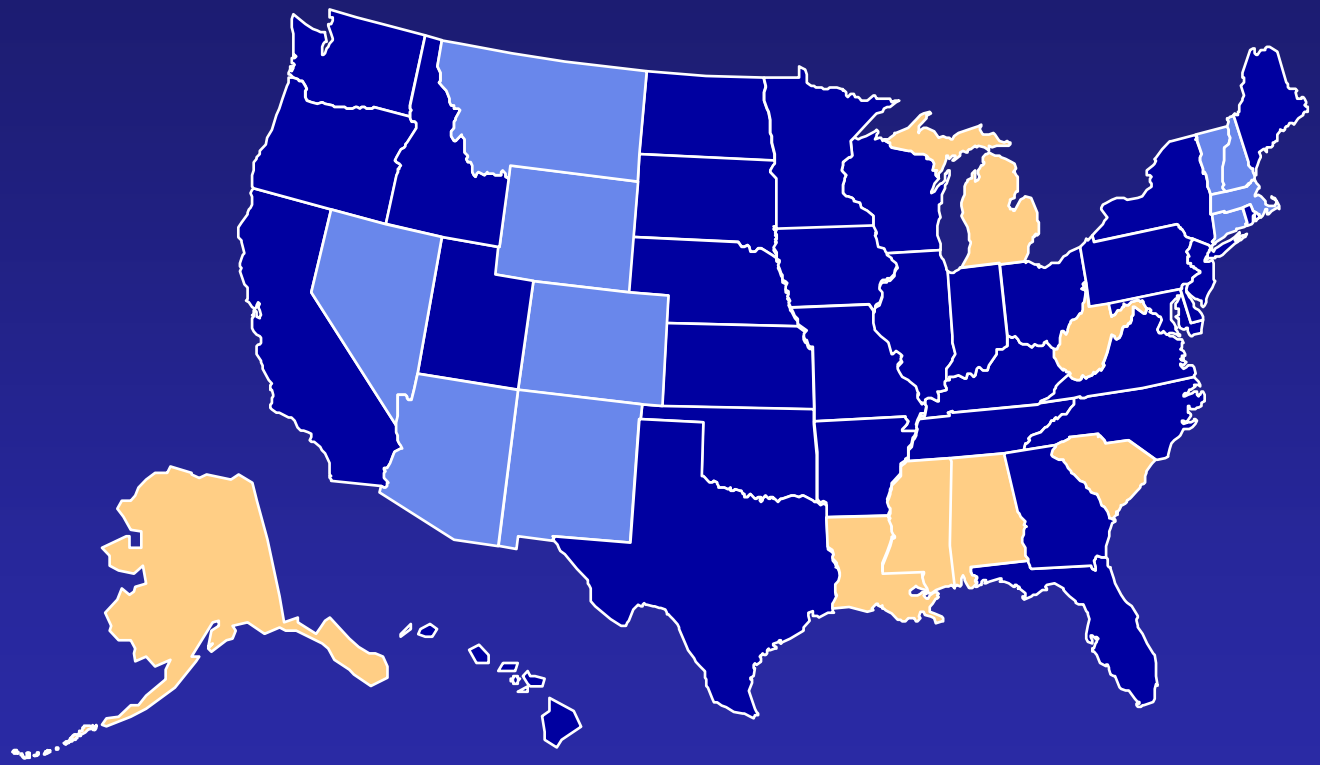


No Data | <10% | 10%–14% | 15%–19% | ≥20%

U.S Obesity Trends 1985-2006, CDC (www.cdc.gov)

Obesity Trends Among U.S. Adults
BRFSS, 1998

BMI ≥30

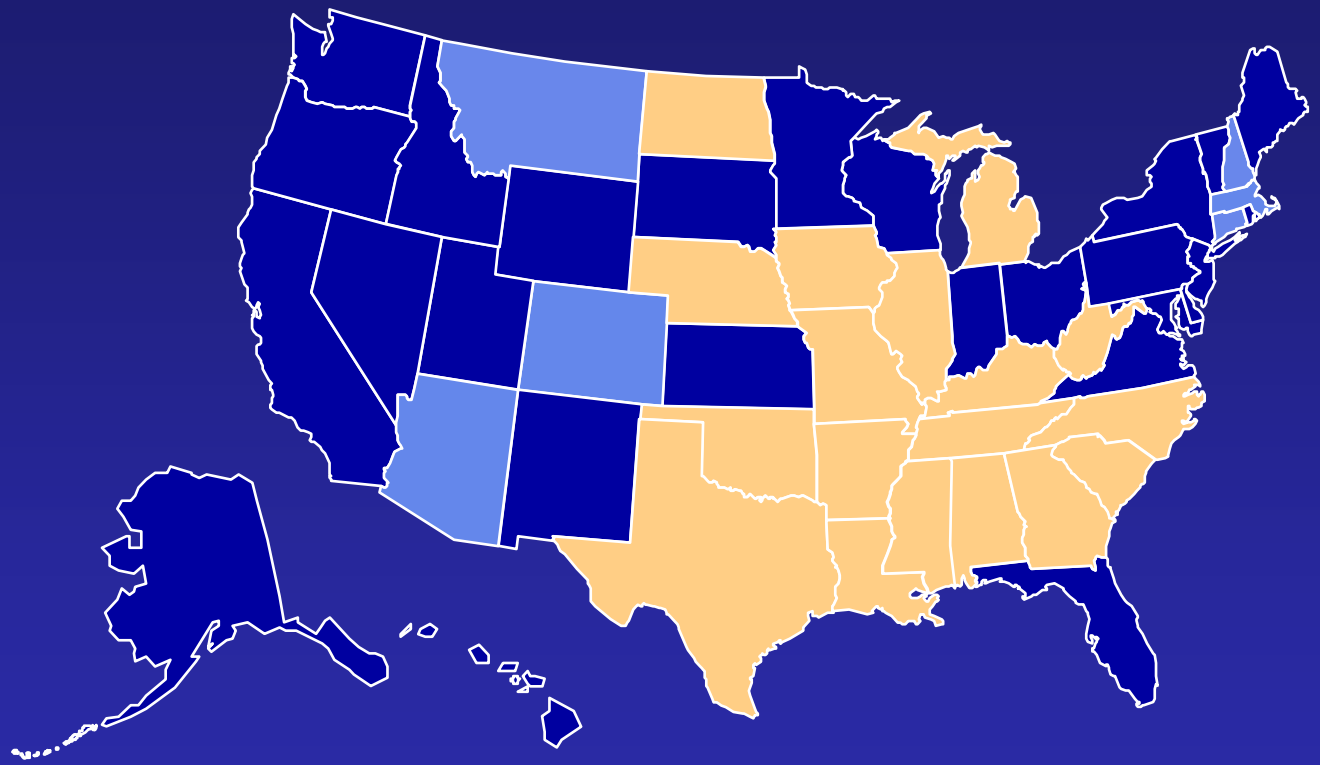


No Data | <10% | 10%–14% | 15%–19% | ≥20%

U.S Obesity Trends 1985-2006, CDC (www.cdc.gov)

Obesity Trends Among U.S. Adults
BRFSS, 1999

BMI ≥30



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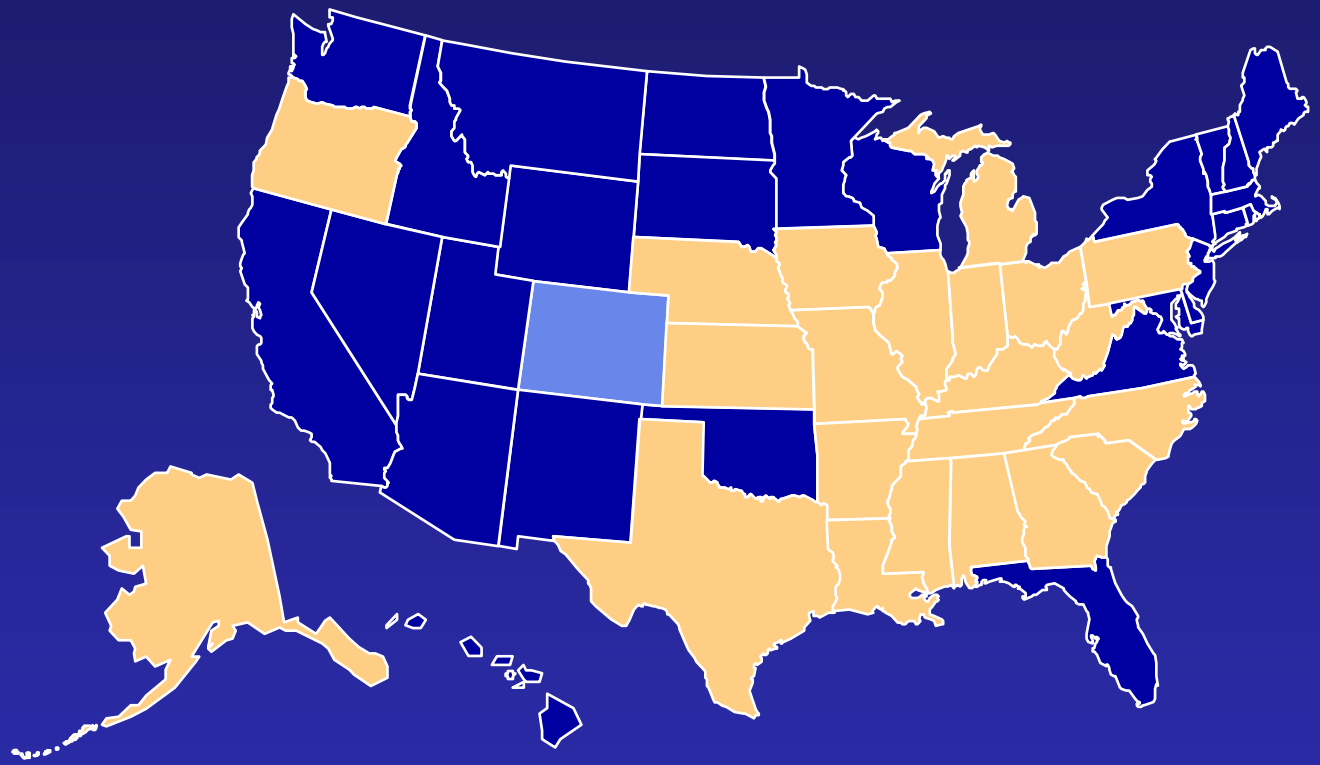
U.S Obesity Trends 1985-2006, CDC (www.cdc.gov)

Obesity Trends Among U.S. Adults
BRFSS, 2000

BMI ≥30



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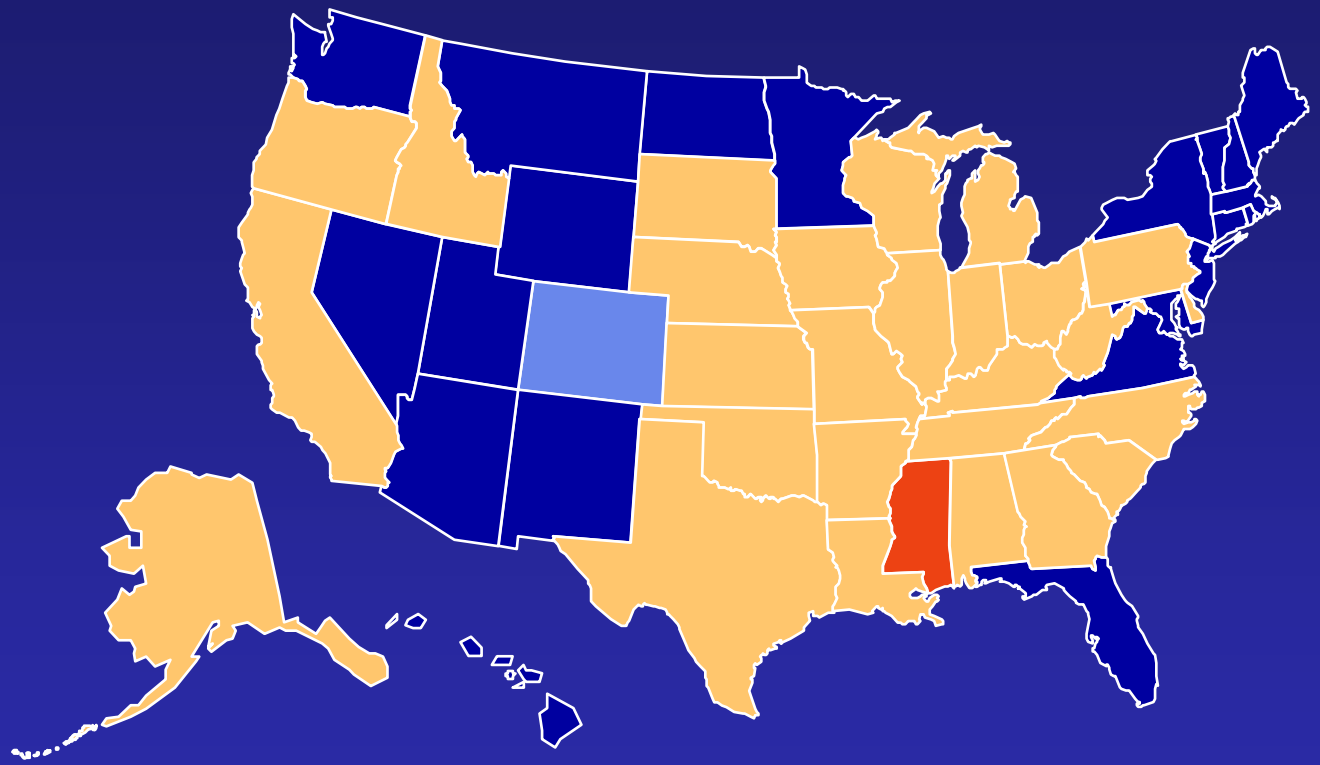
U.S Obesity Trends 1985-2006, CDC (www.cdc.gov)

Obesity Trends Among U.S. Adults
BRFSS, 2001

BMI ≥30



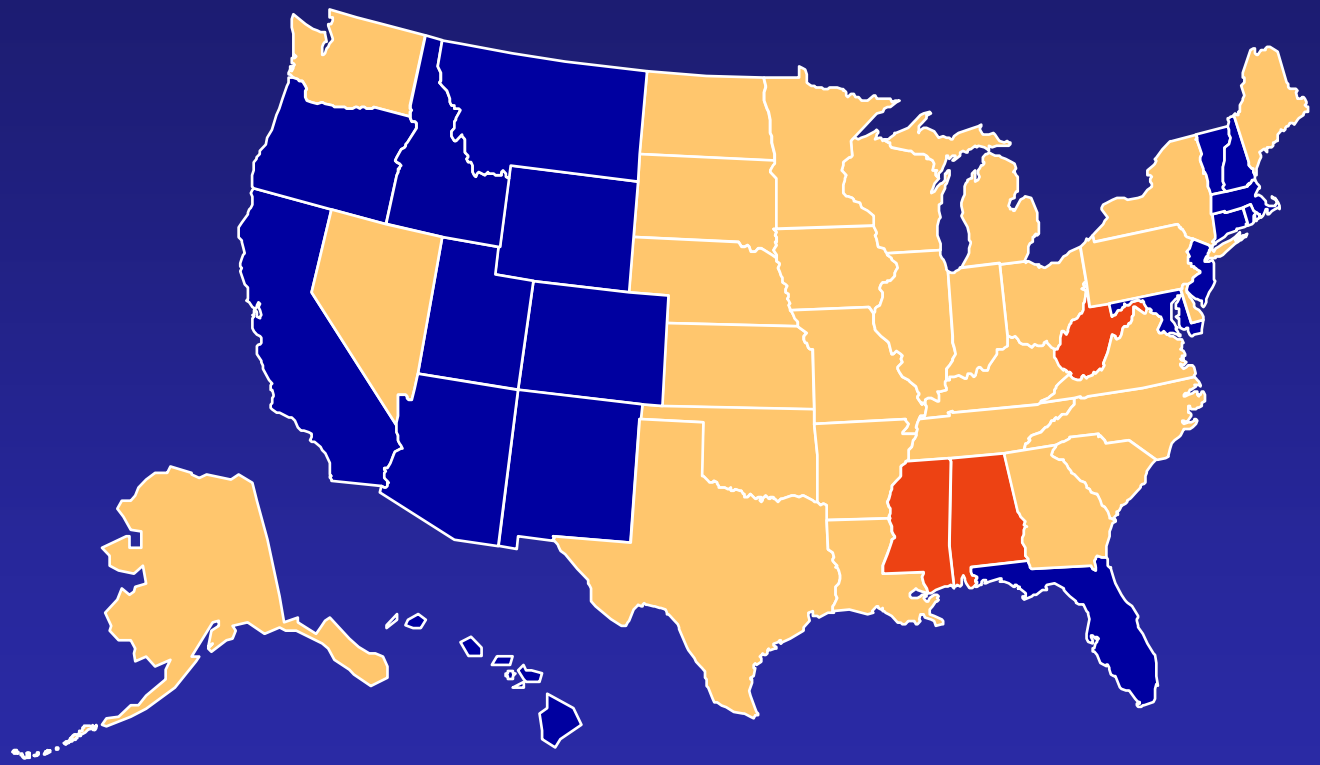
No Data | <10% | 10%–14% | 15%–19% | 20%–24% | ≥25%

U.S Obesity Trends 1985-2006, CDC (www.cdc.gov)

Obesity Trends Among U.S. Adults

BRFSS, 2002

BMI ≥30

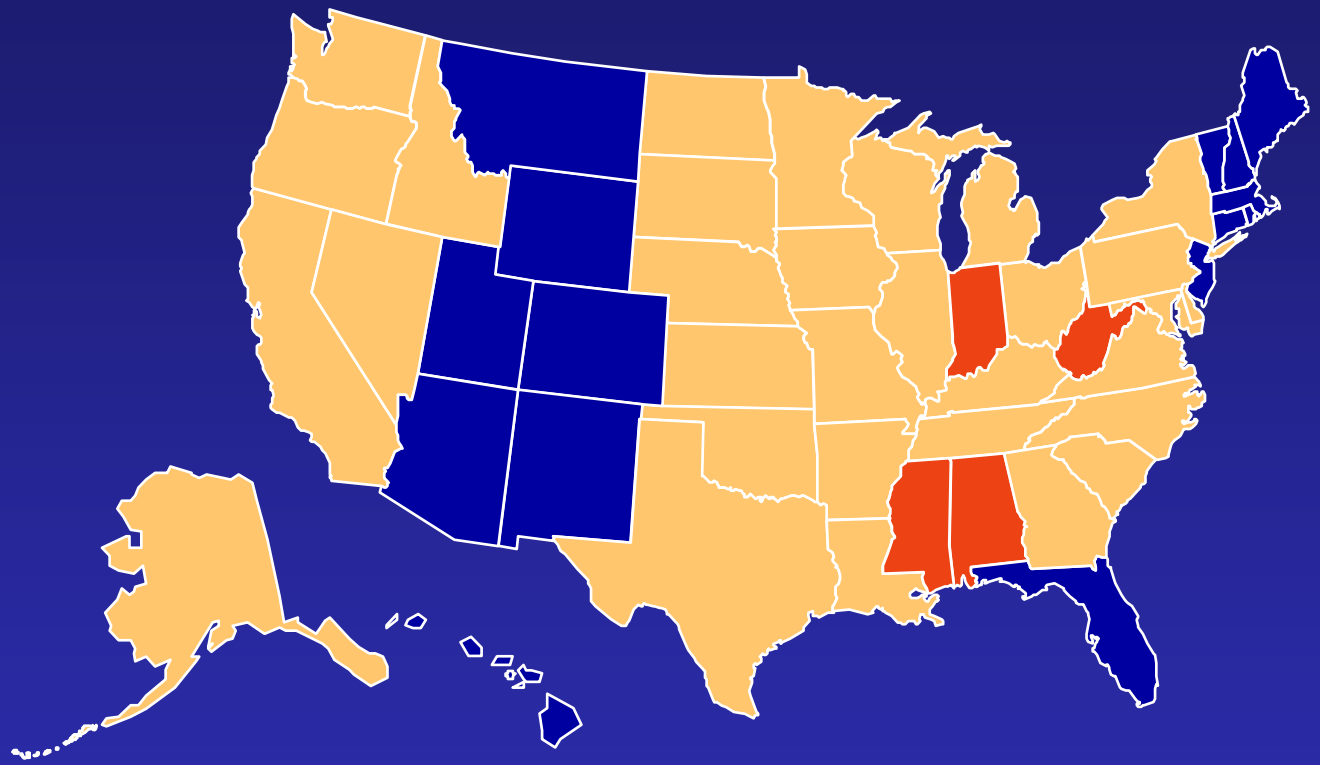


No Data | <10% | 10%–14% | 15%–19% | 20%–24% | ≥25%

U.S Obesity Trends 1985-2006, CDC (www.cdc.gov)

Obesity Trends Among U.S. Adults
BRFSS, 2003

BMI ≥30

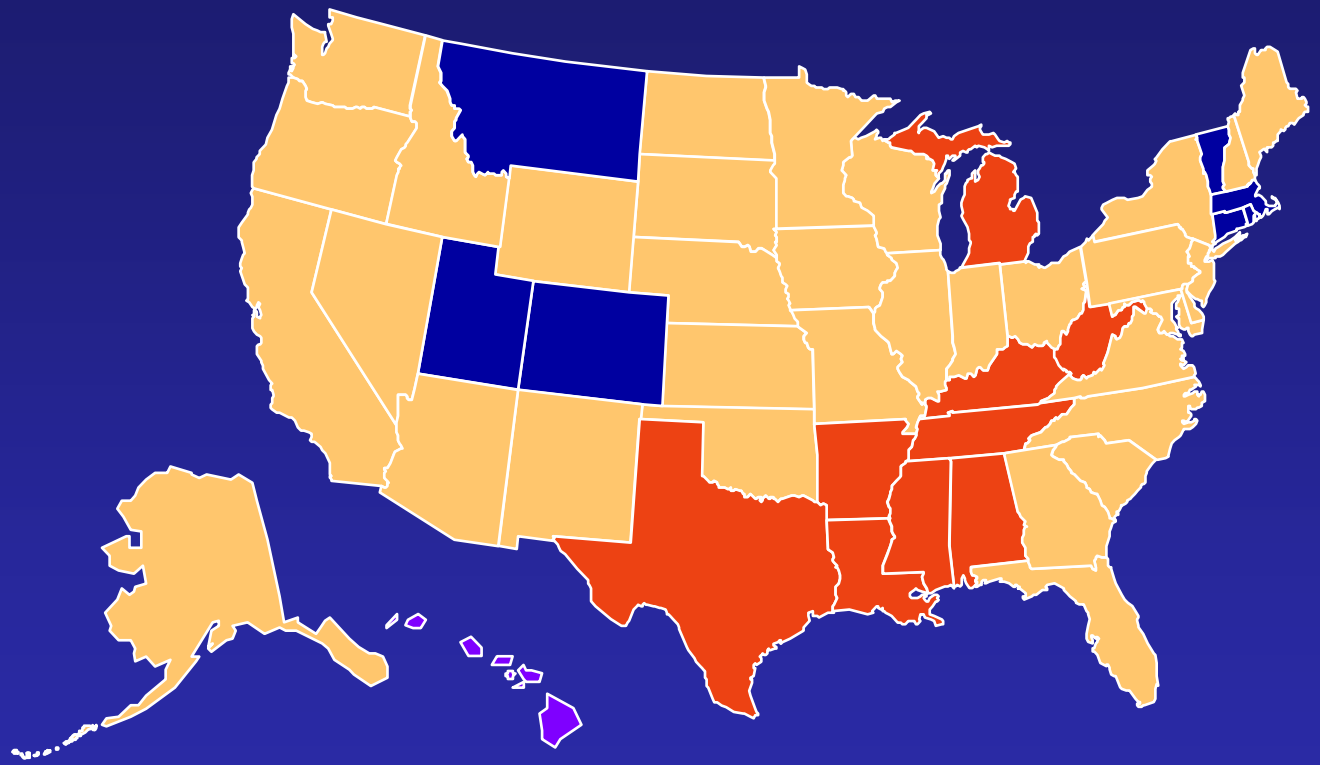


No Data | <10% | 10%–14% | 15%–19% | 20%–24% | ≥25%

U.S Obesity Trends 1985-2006, CDC (www.cdc.gov)

Obesity Trends Among U.S. Adults
BRFSS, 2004

BMI ≥30

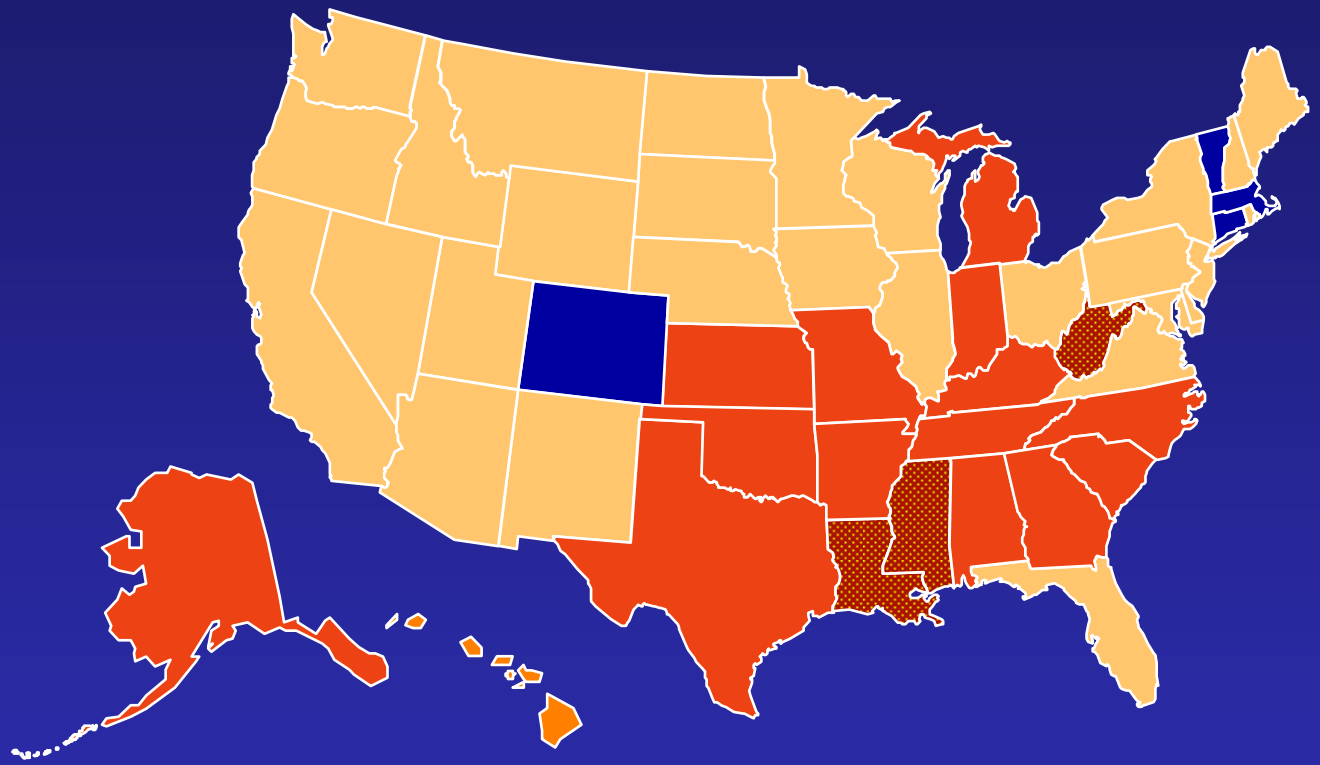


No Data | <10% | 10%–14% | 15%–19% | 20%–24% | ≥25%

U.S Obesity Trends 1985-2006, CDC (www.cdc.gov)

Obesity Trends Among U.S. Adults
BRFSS, 2005

BMI ≥30

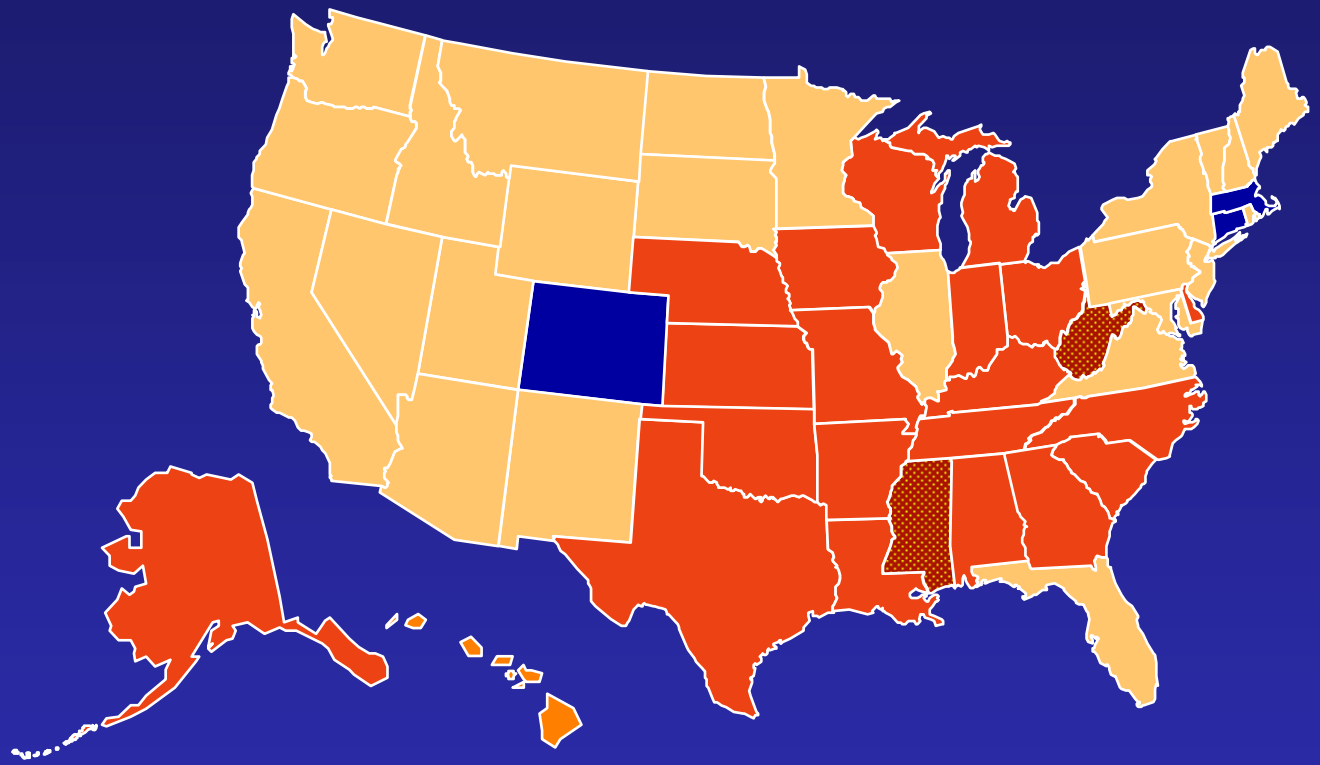


No Data | <10% | 10%–14% | 15%–19% | 20%–24% | 25%–29% | ≥30%

U.S Obesity Trends 1985-2006, CDC (www.cdc.gov)

Obesity Trends Among U.S. Adults
BRFSS, 2006

BMI ≥30

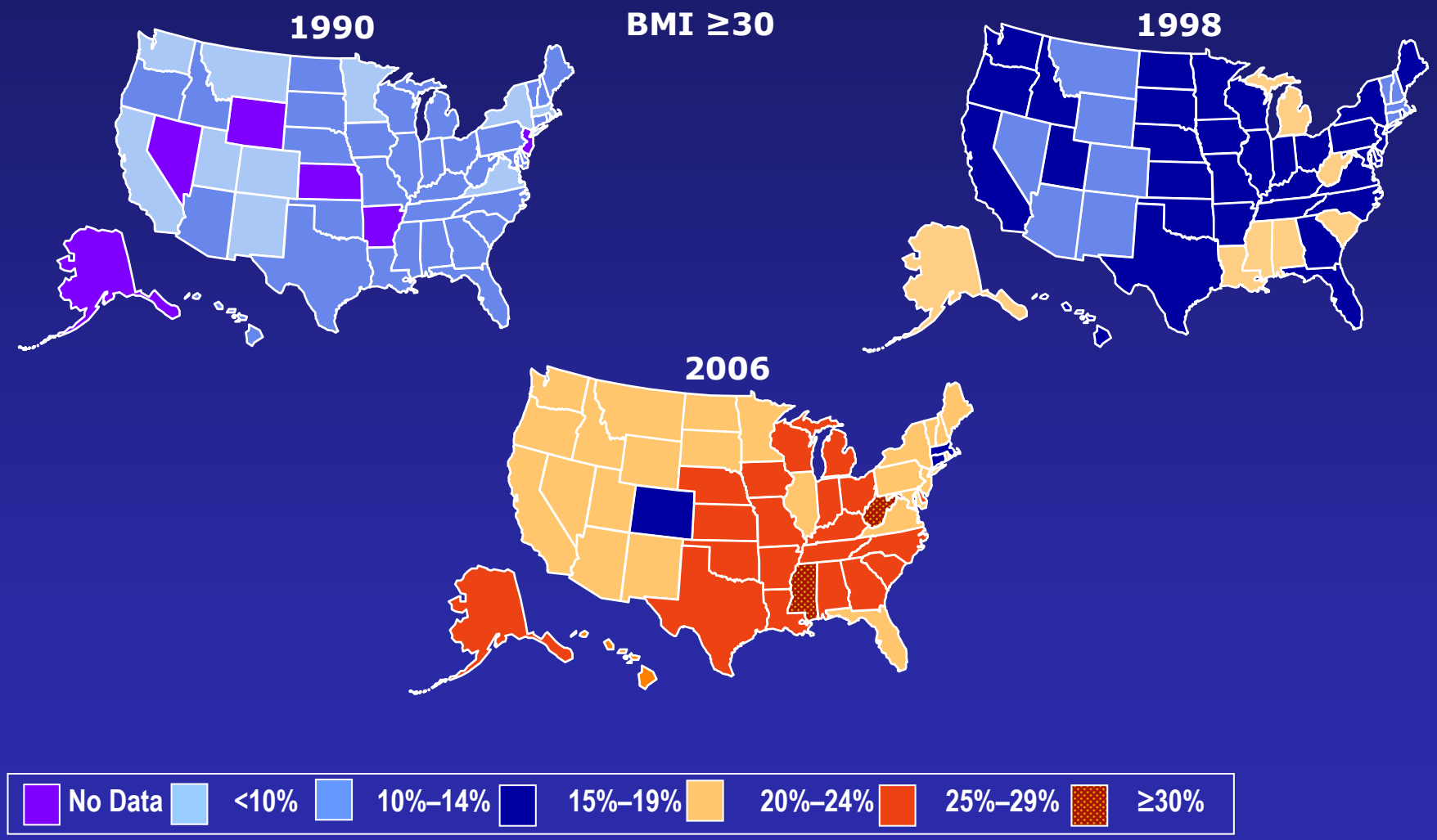


No Data | <10% | 10%–14% | 15%–19% | 20%–24% | 25%–29% | ≥30%

U.S Obesity Trends 1985-2006, CDC (www.cdc.gov)

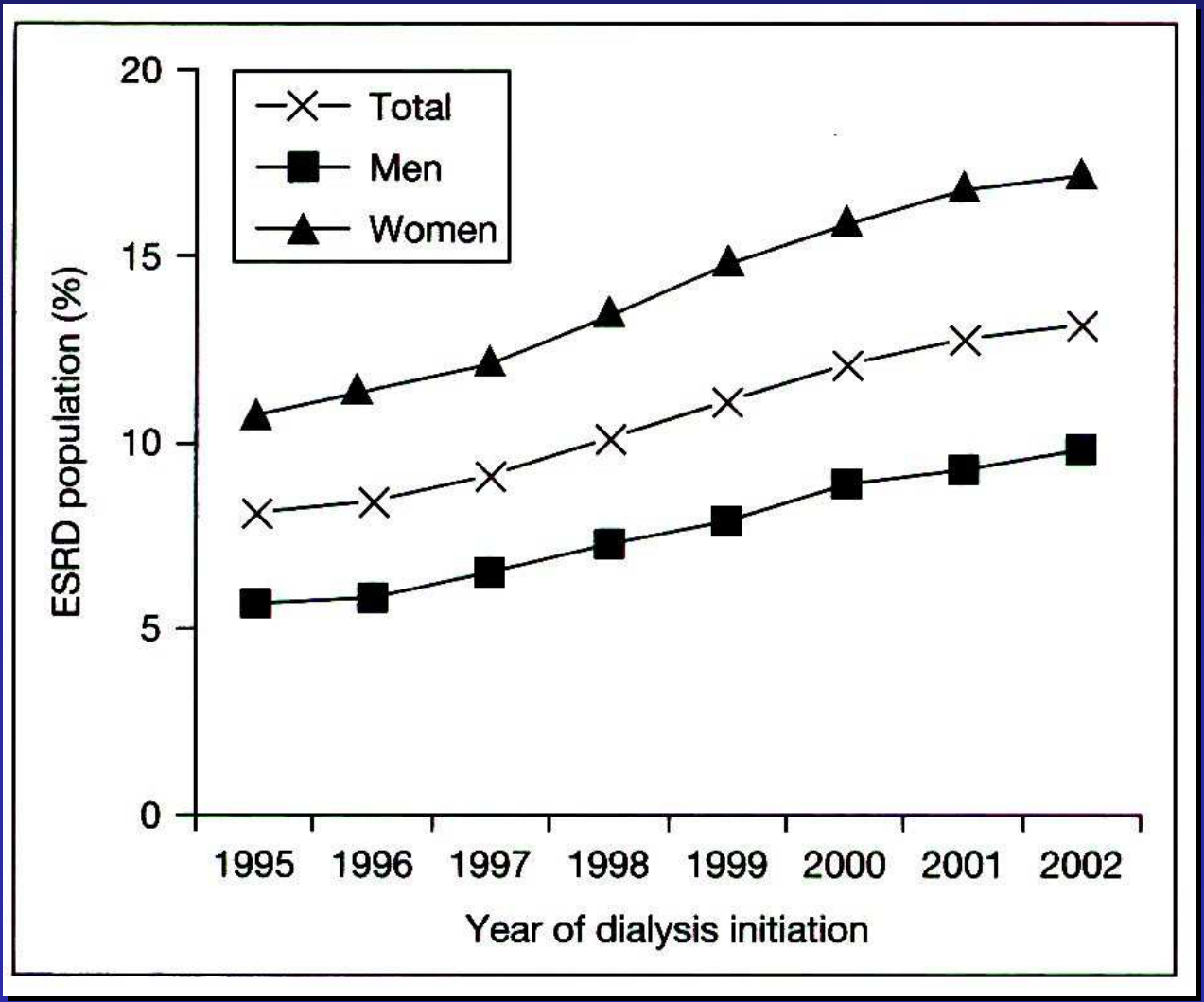
Obesity Trends Among U.S. Adults

Behavioral Risk Factors Surveillance System (BRFSS), 1990, 1998, 2006



U.S Obesity Trends 1985-2006, CDC (www.cdc.gov)

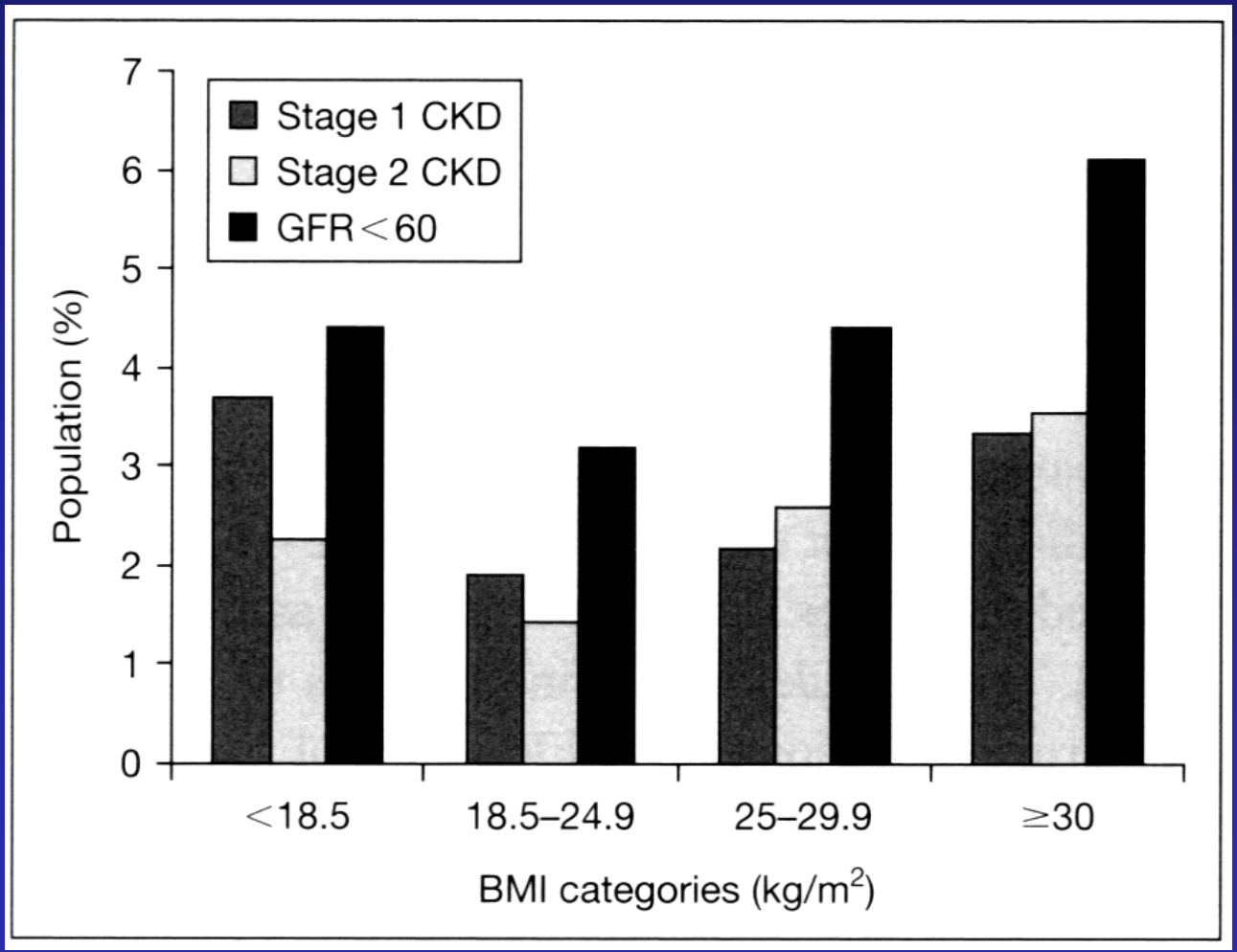
Prevalance of obesity (BMI >30 kg/m2) among incident dialysis patients by year of dialysis inittiation in USA



Kramer H. Contrib Nephrol, 2006:151

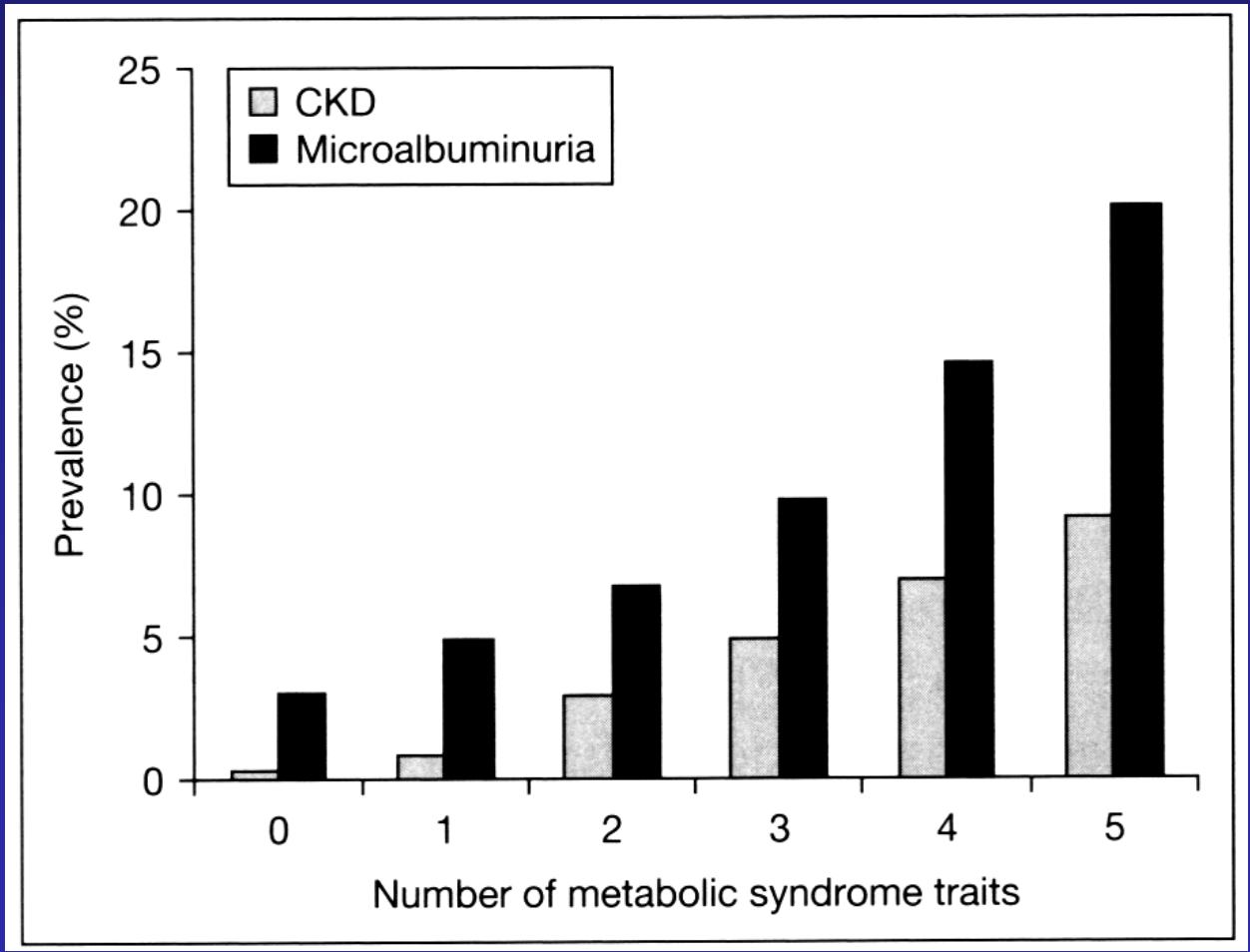
Prevelence of CKD by BMI categories

National Health and Nutrition Examination Survey 1999-2000 (n=5897)



Kramer H., Contrib. Nephrol., 2006, 151, 1-18

Prevelence of CKD (estimated GFR<60 ml/min/1,73) and microalbumionuria by number of metabolic syndrome triats in the non-diabetic U.S population



Kramer H., Contrib. Nephrol., 2006, 151, 1-18

Kidney Int. 2008; 73 18-23

Association between obesity and kidney disease: A systematic review and meta-analysis

Y Wang[1], X Chen[1], Y Song[2], B Caballero[1] and LJ Cheskin[1]

[1]*Center for Human Nutrition, Department of International Health, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland, USA and* [2]*Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA*

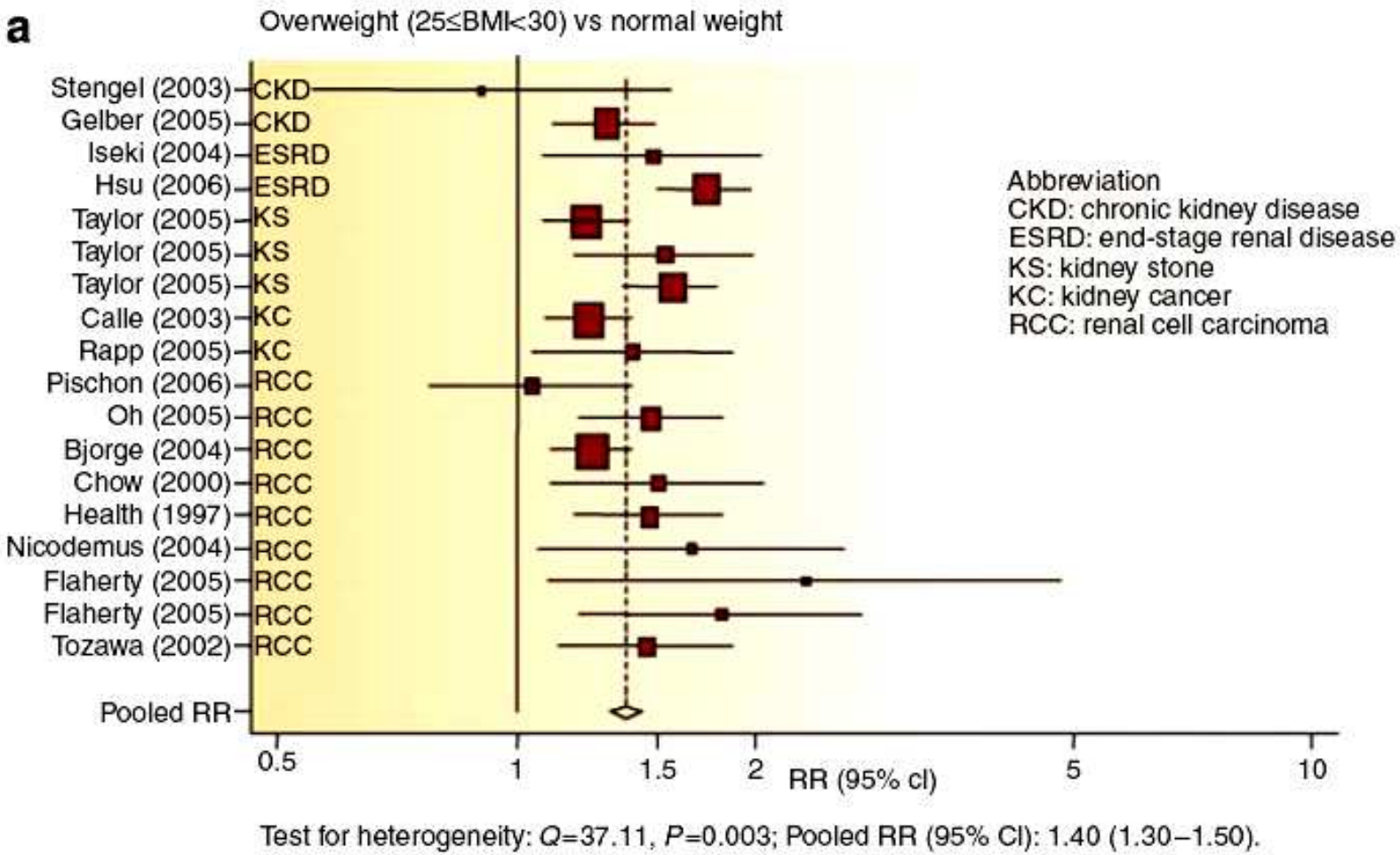
This study aimed to comprehensively assess epidemiologic evidence on the relation between obesity and kidney disease (KD). From 247 retrieved articles via PubMed (1980–2006), 25 cohorts, 3 cross-sectional, and 19 case–control studies met inclusion criteria. Related data were extracted using a standardized protocol. We estimated the pooled relative risk (RR) and 95% confidence interval (95% CI) of KD for each body mass index (BMI) category compared with normal weight using meta-analysis models. Population attributable risk was also calculated. Compared with normal-weight individuals (18.5 < BMI < 25), overweight individuals (25 ⩽ BMI < 30) had elevated risk for KD (RR = 1.40; 95% CI 1.30–1.50); obese individuals were at much higher risk (RR = 1.83 (1.57–2.13)). Obesity in women was associated with a higher risk than in men (RR = 1.92 (1.78–2.07) vs 1.49 (1.36–1.63); *P* < 0.001). Results from cohort studies in patient populations and cross-sectional and case-control studies all indicated a positive association between BMI and risks for KD outcomes. We estimated that 24.2% and 33.9% of KD cases among US men and women, respectively, and in industrialized countries, 13.8% in men and 24.9% in women, could be related to overweight and obesity. Obesity increases the risk for KD in the general population, and the association appears to be stronger in women than in men. Obesity adversely affects the progress of KD among patients with kidney-related diseases.

Kidney International (2008) **73,** 19–33; doi:10.1038/sj.ki.5002586;

Obesity is known to increase the risk of a number of chronic diseases.[1–3] The growing worldwide obesity epidemic has become a public health crisis, affecting many countries. In the United States, obesity is now the second leading cause of preventable disease and death, surpassed only by smoking. There has been increasing interest on the role of the obesity epidemic on risk of kidney disease (KD)[4–6] in part because of the concurrent dramatic rise in the prevalence of end-stage renal disease (ESRD),[7] which has more than doubled in the past decade.[8] The number of patients living with ESRD is projected to reach 650 000 by 2010 in the United States, accounting for $28 billion in medical care expenditures.[9]

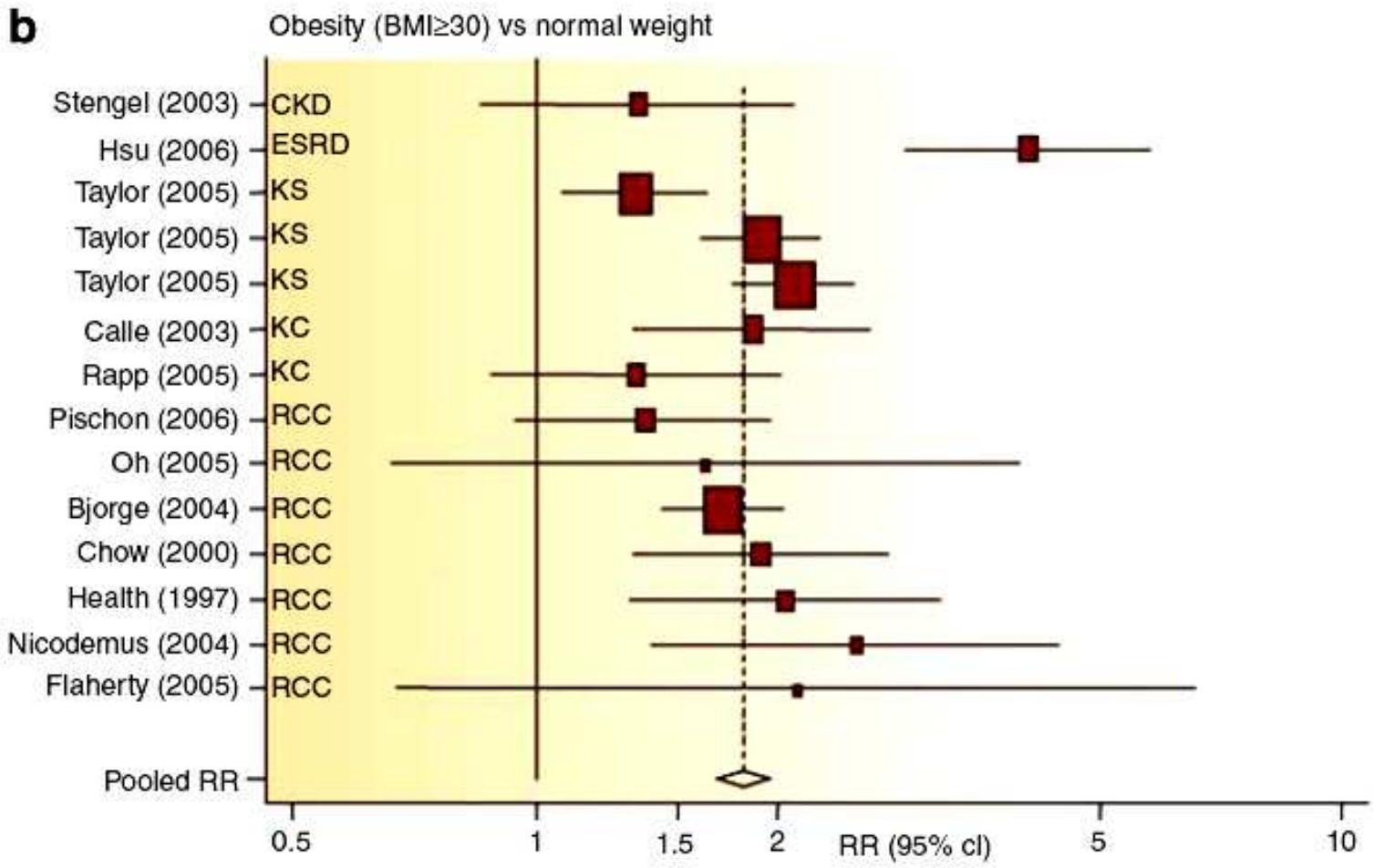
Interventions to prevent KD and its progression to ESRD have the potential to save many lives as well as decrease health-care costs.[10] Identifying modifiable risk factors for KD is critical in order to develop effective, population-based strategies.[11–13] As obesity is closely associated with the two most common causes of ESRD, namely type II diabetes and hypertension, it may increase the risk of ESRD.[14–17] Available data suggest that the incidence of some KD outcomes vary greatly across different regions of the world that have different prevalence of obesity, suggesting that obesity may be an important risk factor for KD.[18–22] For example, the incidence of renal cell cancer (RCC) varies more than 10-fold in different regions of the world. It is the highest in North America, and lowest in Asia.[23] Two major obstacles to prospectively studying risk

Association between overweight and kidney disease based on cohort studies in the general populations - overweight (25>BMI<30) vs normal weight.



Wang Y. et al., Kidney Int., 2008; 73 18-23

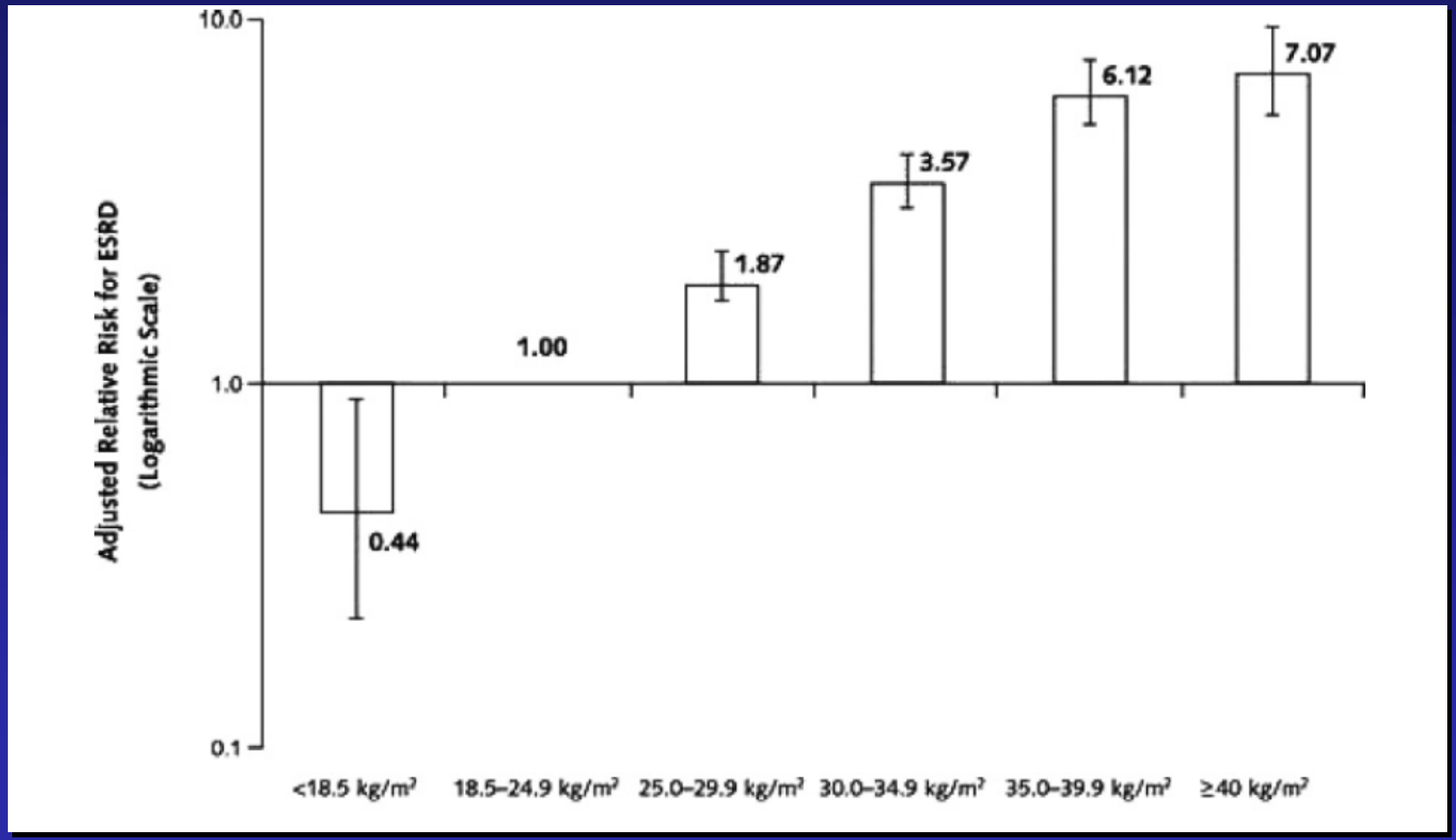
Association between obesity and kidney disease based on cohort studiesin the general populations – obesity (BMI>30) vs normal weight.



Test for heterogeneity: Q=40.96, P=0.001; Pooled RR (95% CI): 1.83 (1.57–2.13).

Wang Y. et al., Kidney Int., 2008; 73 18-23

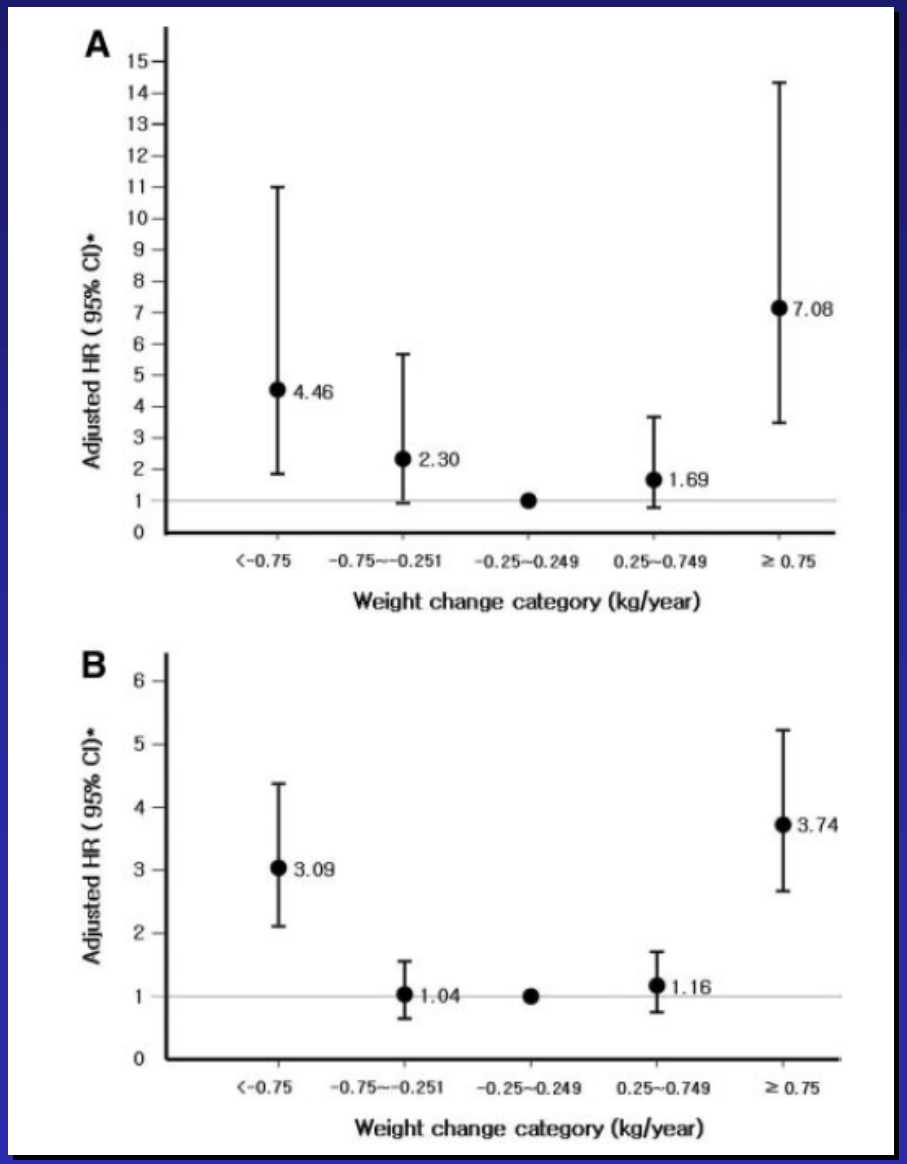
Adjusted relative risk for end-stage renal disease (ESRD) by body mass index (BMI)



Model adjusted for multiphasic health checkup period, age, sex, race, education level, smoking status, history of myocardial infarction, serum cholesterol level, proteinuria, haematuria and serum creatinine evel.

Hsu et al. Ann Intern Med. 2006; 144: 21–28

Association between the development of CKD (estimated GFR 64 ml/min per 1.73 m2) and weight change per year - HR increase even among patients with normal BMI !



baseline BMI between 18.5 and 23.0 kg/m2

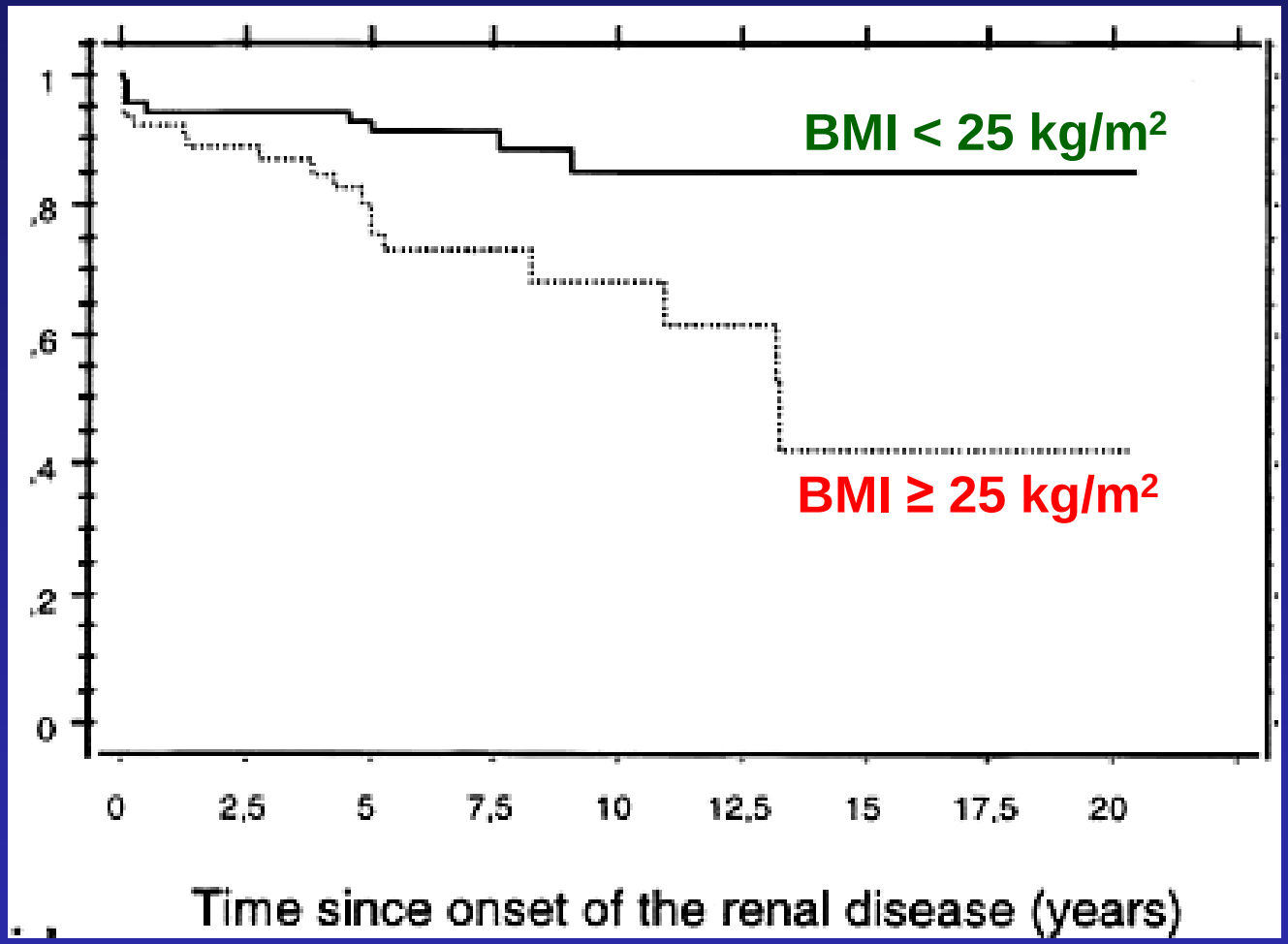
baseline BMI >23.0 kg/m2

Adjustment for age, baseline GFR, BMI, HDL , cholesterol,

FBG, uric acid, and regular exercise ■

Ryu S., J Am Soc Nephrol. 2008 May 21

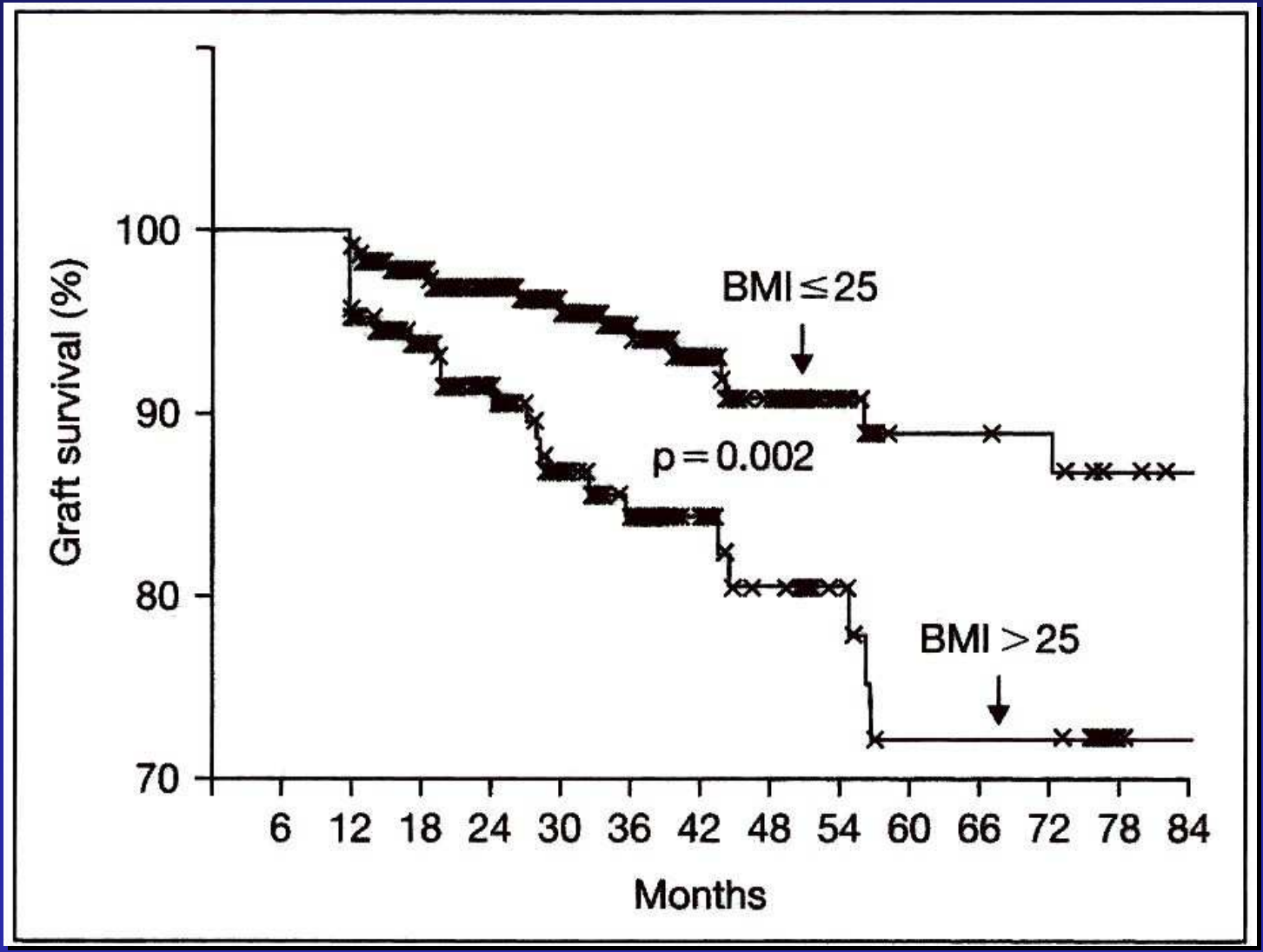
Overweight significantly increase risk of IgA nephropathy progression



CRF-free survival rate according to the presence of an elevated BMI at the initial renal biopsy.

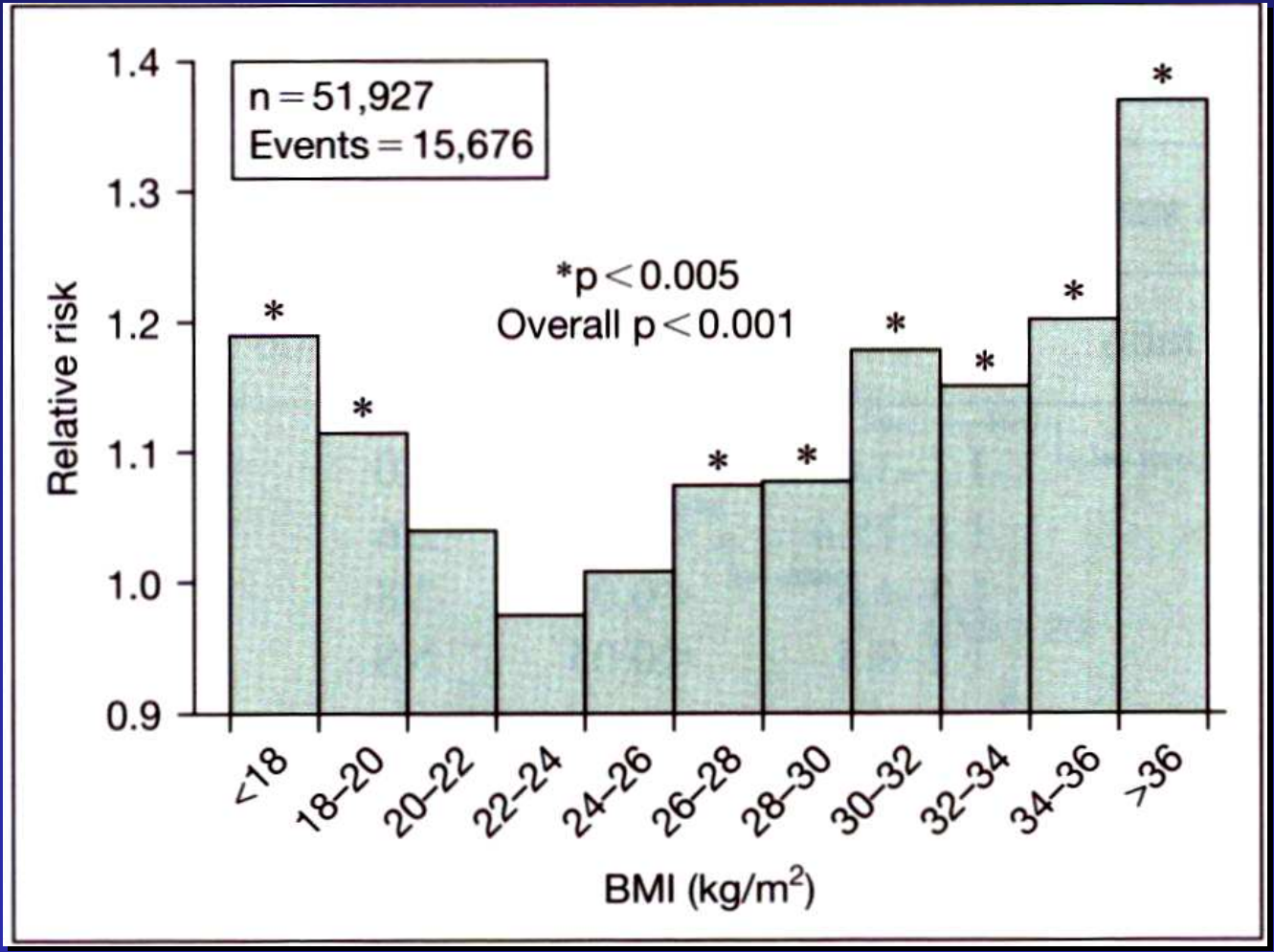
Bonnet F et al., Am. J. Kidney Dis., 2001, 37: 720-727

Graft survival analysis.



Srinivals and Meier-Kriesche. Contrib Nephrol, 2006:151

Relative risk for graft loss by BMI



Srinivals and Meier-Kriesche. Contrib Nephrol, 2006:151

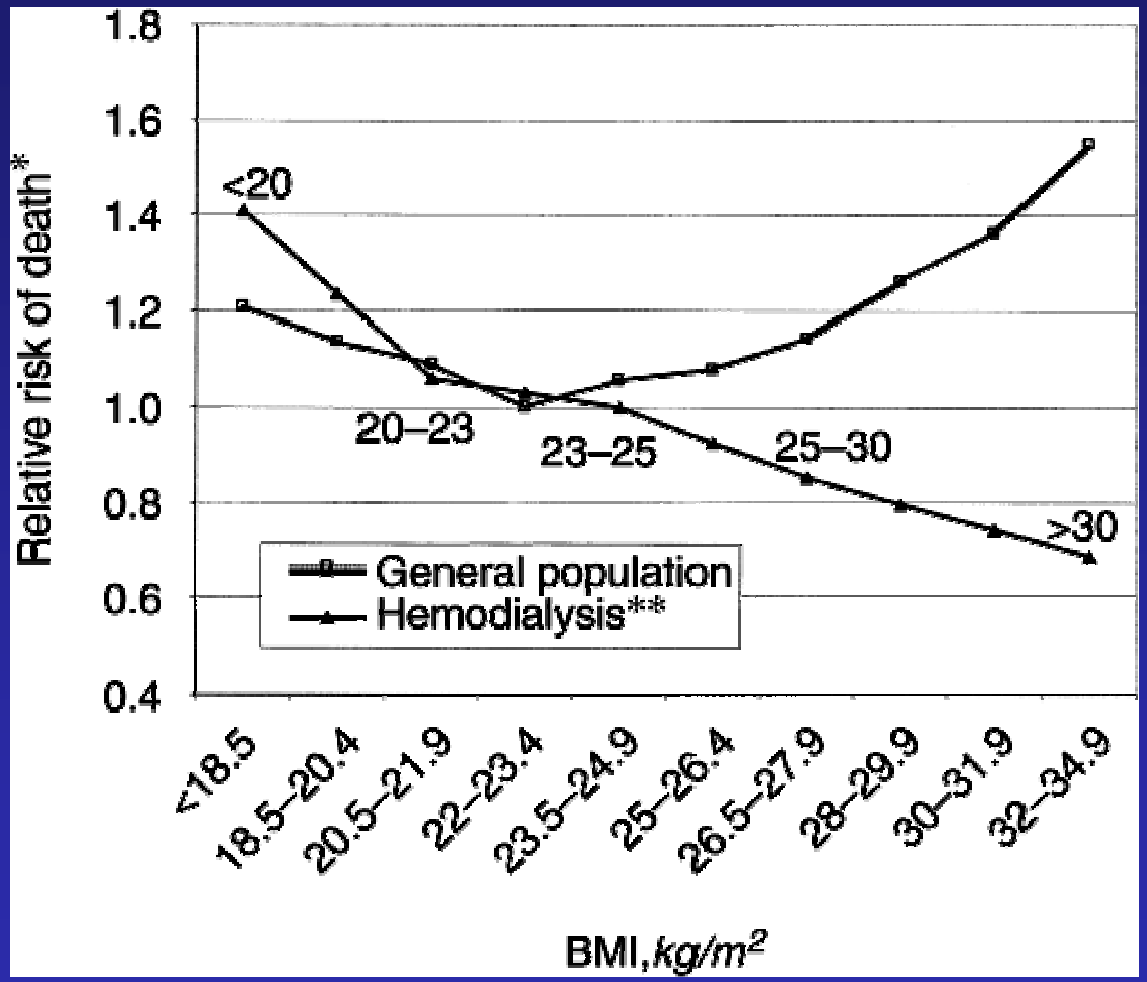
The relationship between obesity and stage 3 CKD may be mediated through cardiovascular disease risk factors

Obese individuals had a 68% increased odds of developing stage 3 CKD (OR, 1.68; 95% CI, 1.10 to 2.57; *p=0.02), which became* nonsignificant in multivariable models (OR, 1.09; 95% CI, 0.69 to 1.73; *p=0.7)*

Model	Sample Size/No. of Patients With CKD	BMI Category	OR (95% CI)	*P*	*P* for Trend
Overall	2,676/212				
Age- and sex-adjusted*		Overweight	1.29 (0.93-1.81)	0.1	0.01
		Obese	1.68 (1.10-2.57)	0.02	
Multivariable-adjusted†		Overweight	1.06 (0.75-1.50)	0.8	0.7
		Obese	1.09 (0.69-1.73)	0.7	
Hypertension free	2,147/126				
Age- and sex-adjusted*		Overweight	1.09 (0.72-1.67)	0.7	0.1
		Obese	1.70 (0.95-3.03)	0.07	
Multivariable-adjusted†		Overweight	0.91 (0.59-1.41)	0.7	0.7
		Obese	1.10 (0.59-2.06)	0.8	
Diabetes free	2,632/196				
Age- and sex-adjusted*		Overweight	1.31 (0.93-1.84)	0.1	0.2
		Obese	1.25 (0.78-2.01)	0.4	
Multivariable-adjusted†		Overweight	1.10 (0.77-1.56)	0.6	0.8
		Obese	0.87 (0.53-1.44)	0.6	
Free of prevalent CVD	2,626/197				
Age- and sex-adjusted*		Overweight	1.32 (0.93-1.86)	0.1	0.009
		Obese	1.77 (1.15-2.73)	0.01	
Multivariable-adjusted†		Overweight	1.05 (0.73-1.52)	0.8	0.7
		Obese	1.10 (0.69-1.77)	0.7	

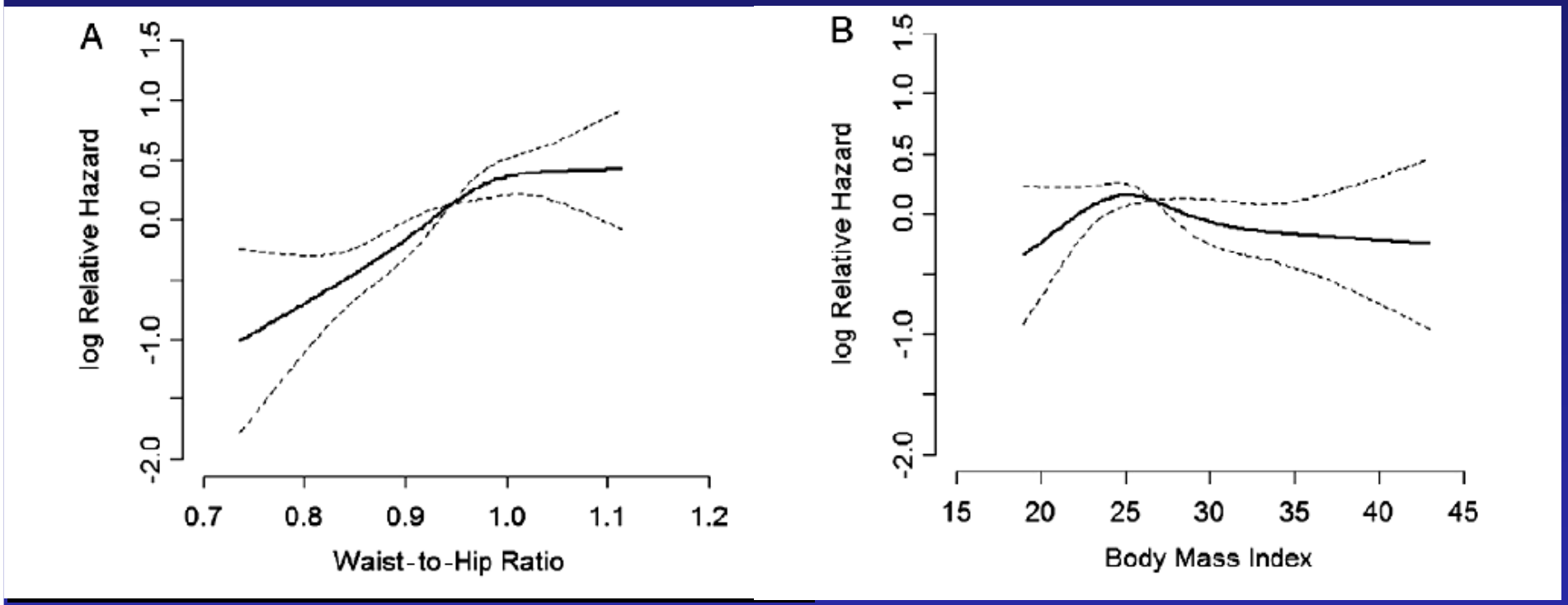
Foster M C et al., Am J Kidney Dis. 2008, 52, 39-48.

Comparison between the impact of body mass index (BMI) on all-cause mortality in the general population versus the maintenance hemodialysis population – OBESITY PARADOX



Kalantar - Zadeh K., Kidney Int., 2003, 63, 793-808

WHR, but not BMI, is associated with cardiac events in patients with CKD



Elsayed E et al. Am J Kidney Dis. 2008, 52 :49-57.

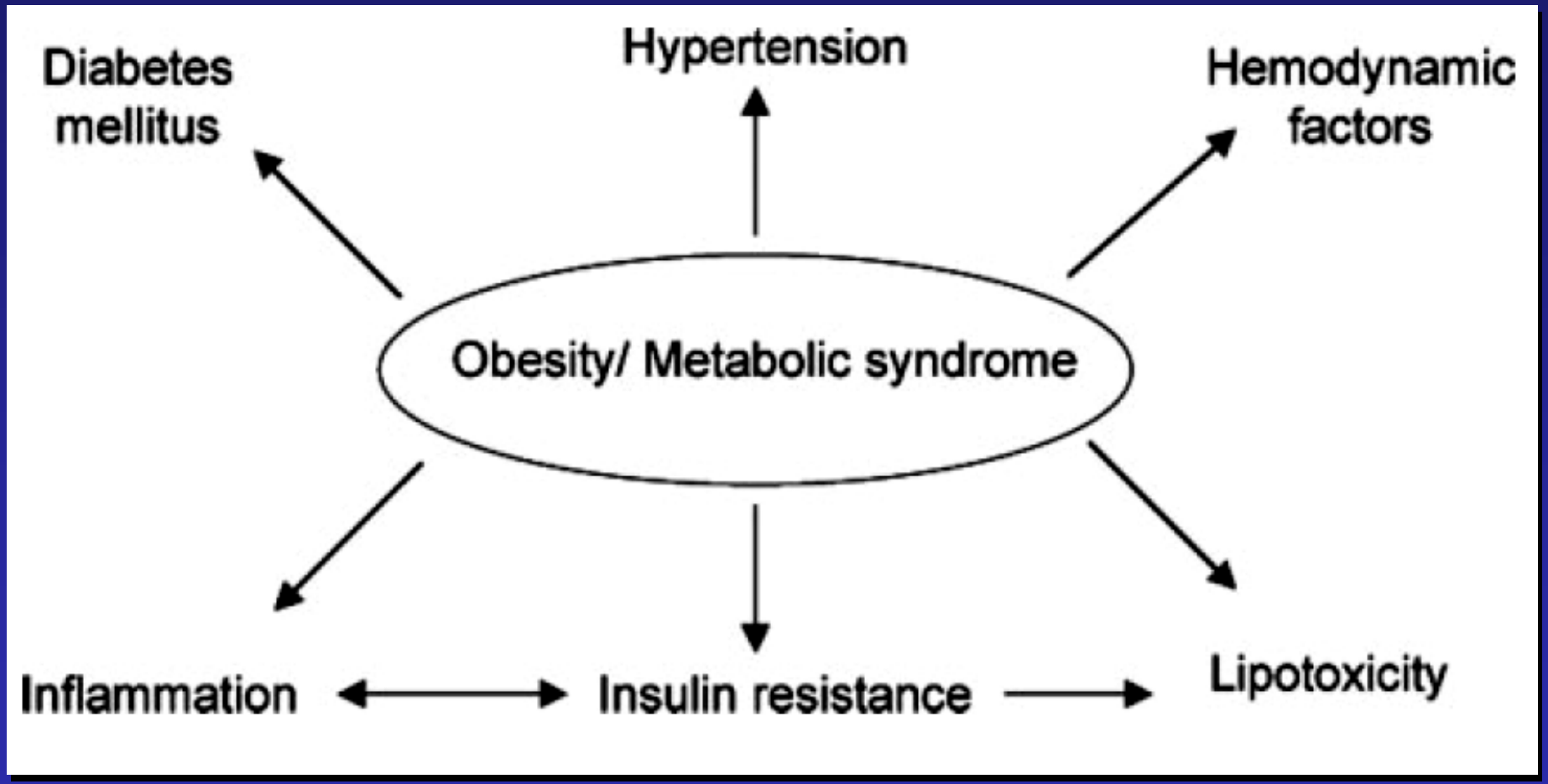
Population attributable risk (PAR) of KD due to overweight and obesity in the United States and industrialized countries – elimination of overweight and obesity can decrease incidence of kidney disease about 30%

	USA[b]			Industrialized countries[c]		
	All	Men	Women	All	Men	Women
Prevalence (%)						
Overweight	34.1	39.7	28.6	33.6	38.1	29.3
Obesity	32.2	31.1	33.2	16.6	12.9	20.1
PAR (%) of overall KD						
Overweight	12.0	11.0	10.5	11.8	10.6	10.7
Obesity	21.1	13.2	23.4	12.1	5.9	15.6
Total	33.1	24.2	33.9	24.0	16.5	26.3
PAR (%) of non-kidney cancer/RCC						
Overweight	12.5	19.0	12.1	12.4	18.4	12.3
Obesity	23.4	9.3	24.7	13.6	4.1	16.6
Total	36.0	28.3	36.8	26.0	22.4	28.9
PAR (%) of kidney cancer/RCC						
Overweight	9.6	7.7	9.8	9.4	7.4	10.0
Obesity	18.6	14.2	22.4	10.5	6.4	14.9
Total	28.2	21.8	32.2	20.0	13.8	24.9

IOTF, International Obesity Task Force; KD, kidney disease; NHANES, National Health and Nutrition Examination Surveys; PAR, population attributable risk; RCC, renal cell carcinoma.
[a]RRs were based on our meta-analysis (see Table 3).
[b]Prevalence estimates were based on NHANES 2003–2004 data.[26]
[c]Prevalence estimates were based on IOTF's estimates.

Wang Y, et al., Kidney Int., 2008; 73 18-23

Potential mechanisms of renal injury in patients with obesity and obesity initiated metabolic syndrome



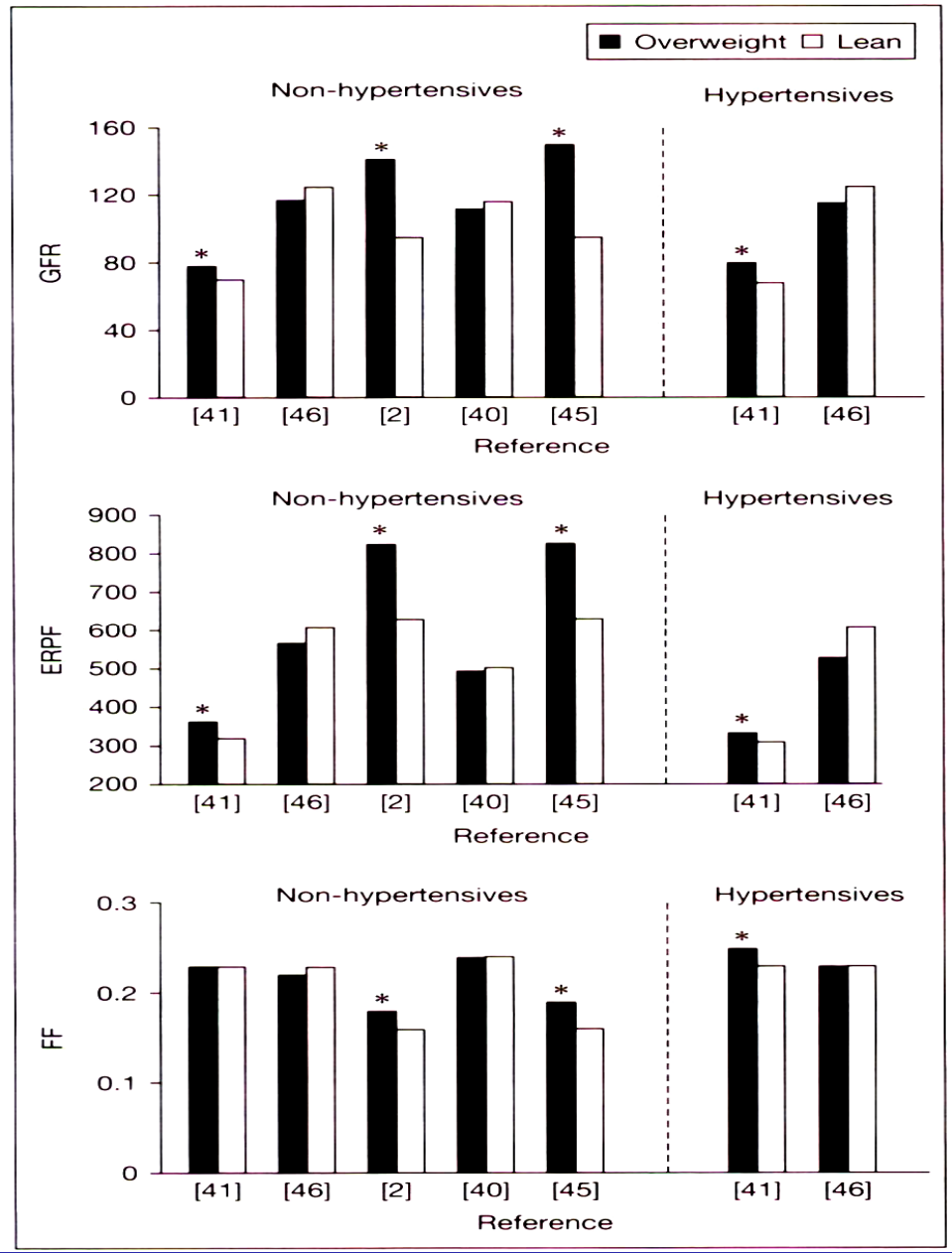
Wahba I.M. et al. Clin. J .Am. Soc. Nephrol., 2007; 2: 550-562

Hemodynamic factors: Obesity and renal hemodynamic

GFR

ERPF

FF



Studies showing the impact of overweight and obesity on GFR,ERPF, FF

Bosma et al. Contrib Nephrol, 2006:151

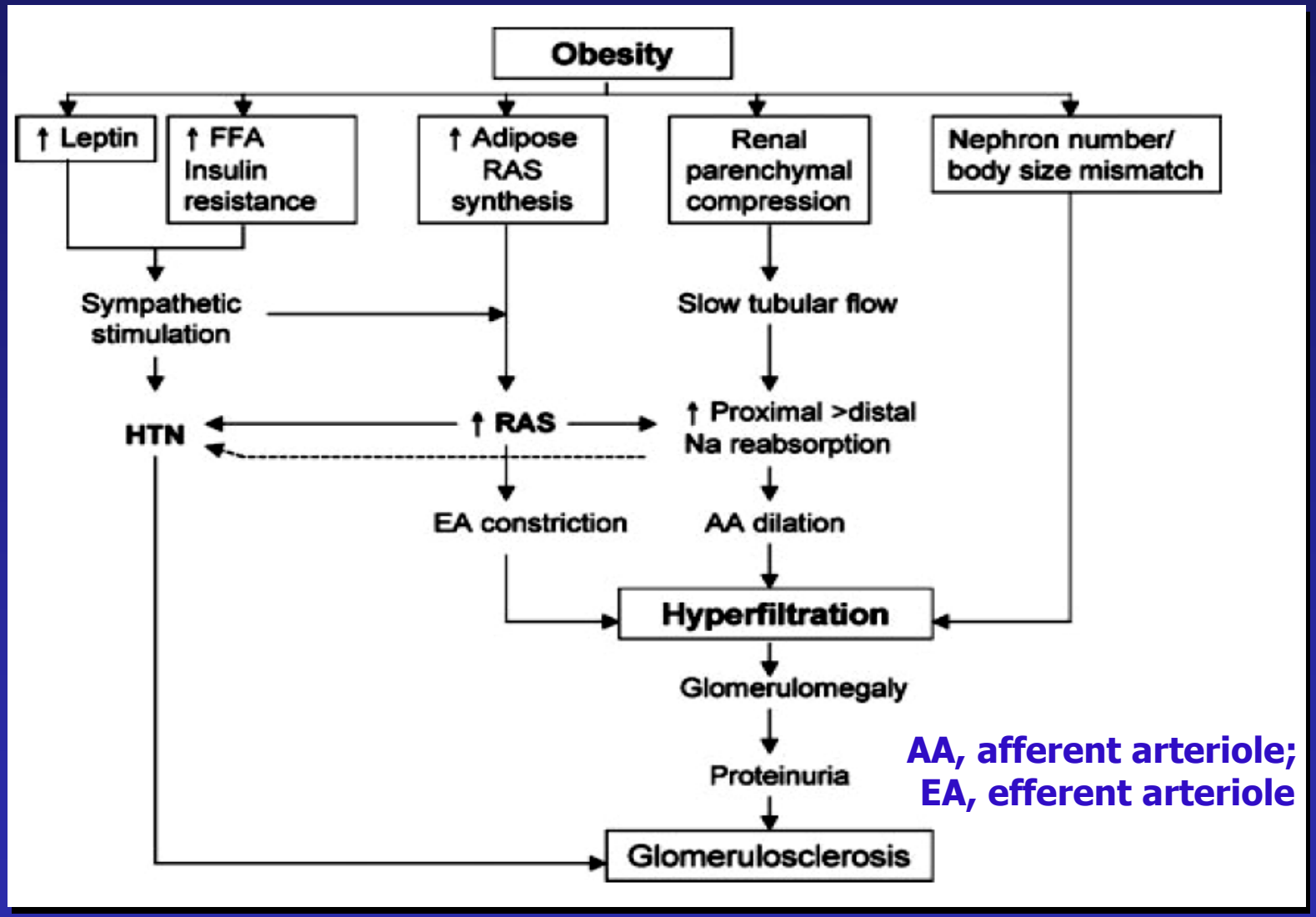
Obesity and ranal hemodynamic, renal reabsorbtion and neurohormonal activity

Model	Arterial pressure	Heart rate	Cardiac output	Renal sympathetic activity	Plasma renin activity	Na^+ balance	Renal tubular reabsorption	GFR[a]
Obese rabbits (high fat diet)	↑	↑	↑	↑	↑	↑	↑	↑
Obese dogs (high fat diet)	↑	↑	↑	↑	↑	↑	↑	↑
Obese humans	↑	↑	↑	↑	↑	↑	↑	↑

GFR, glomerular filtration rate. [a]The GFR changes refer to the early phases of obesity before major loss of nephron function has occurred.

Hall J.E. et al., Curr. Opin. Nephrol. Hypertens. 2003, 12: 195 -201

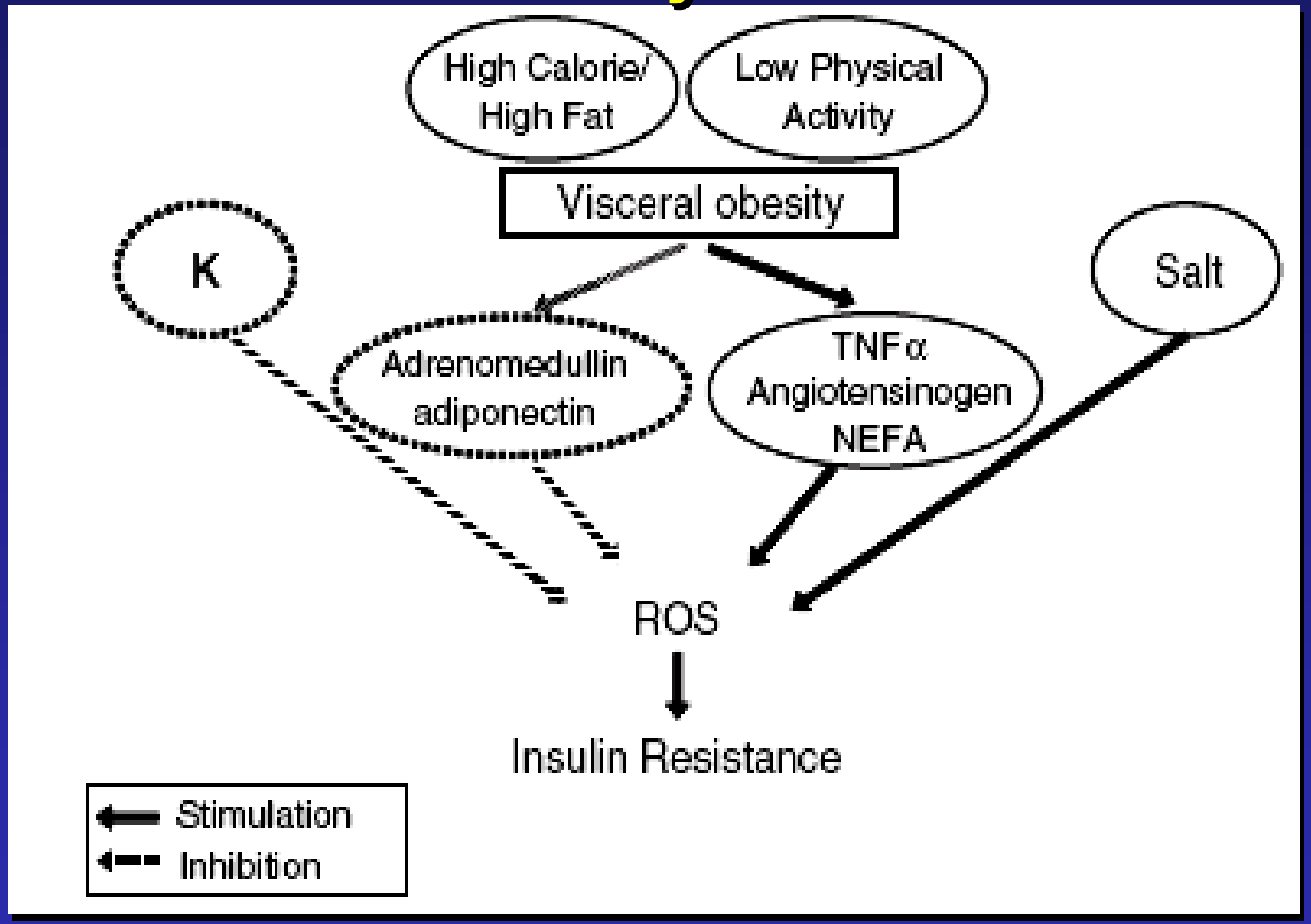
Hemodynamic consequences of obesity leading to hyperfiltration and hypertension



AA, afferent arteriole;
EA, efferent arteriole

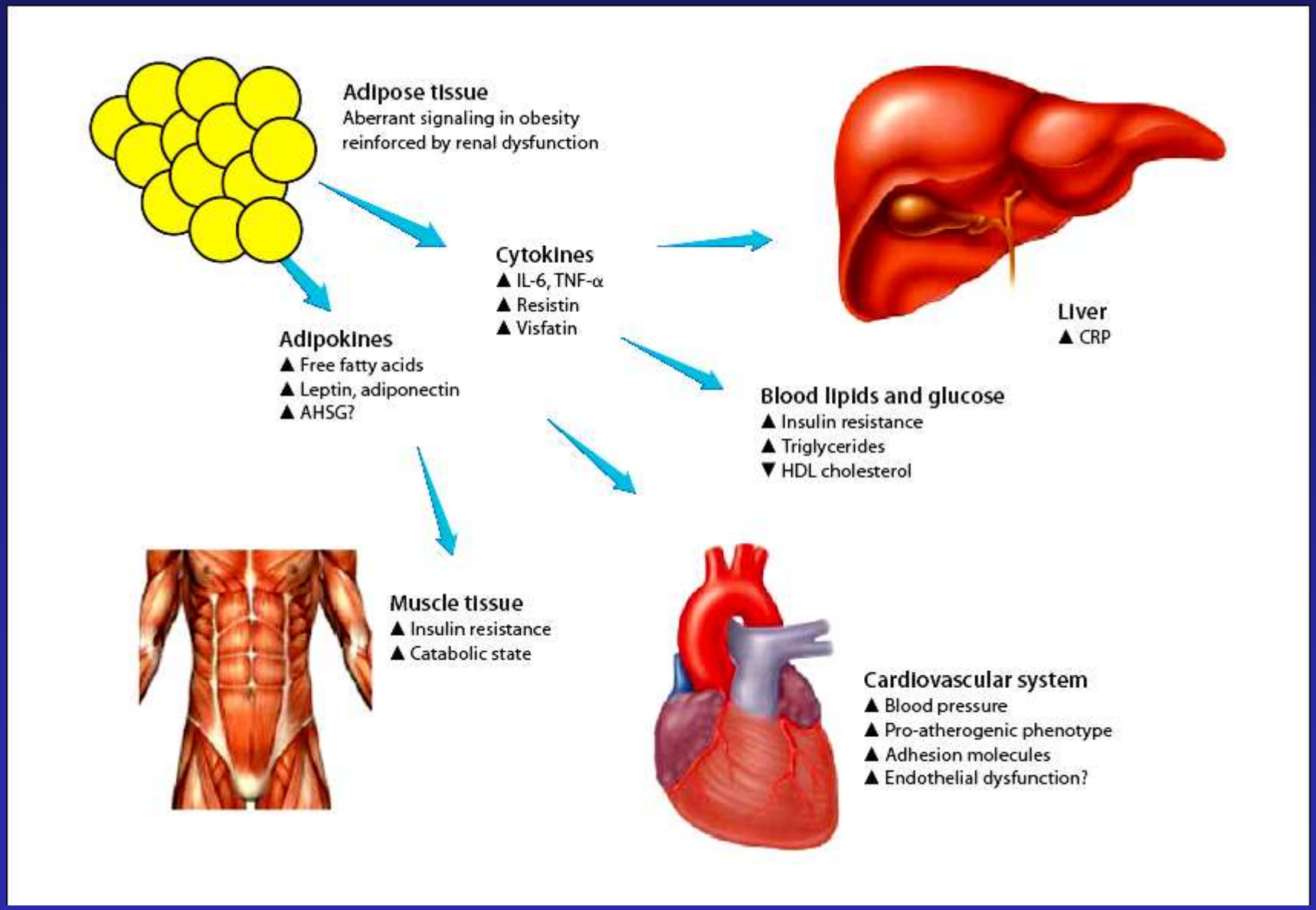
Wahba I.M. et al. Clin. J. Am. Soc. Nephrol., 2007; 2: 550-562

Mechanism for insulin resistance in metabolic syndrome



Fujita T. Nephrol. Dial.Transplant., 2007; 22: 3102-3107

Adipose tissue as an endocrine organ



Axelsson J., Blood Purif., 2008; 26: 23-29

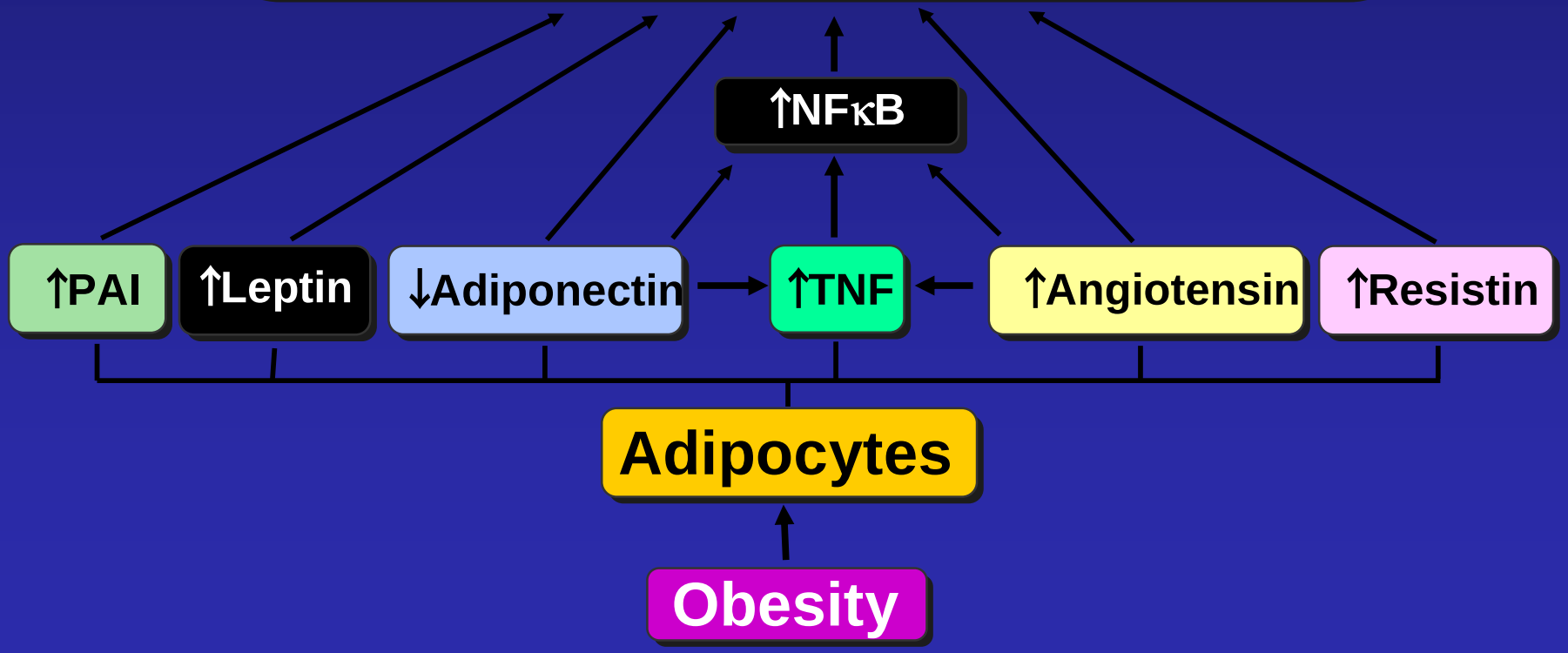
Biologically active substances with local and /or systemic action produced by adipose tissue (1)
(The mature adipocytes: a highly specialized endocrine cells)

- Apelin
- Obestatin
- PA I-1
- TGF-β
- Tissue factor (TF)
- Complement factors (e.g. adipsin)
- TNF-α
- Acylation stymulation protein (ASP)
- Agouti Protein
- Angiotensinogen, Renin, ACE
- Chymase, cathepsin D,G
- Angiotensin II
- Prostaglandins (PGI2, PGF2α)
- Insulin growth factor-1 (IGF1)

Biologically active substances with local and /or systemic action produced by adipose tissue (2)
(The mature adipocytes: a highly specialized endocrine cells)

- Vascular endothelial growth factor (VEGF)
- Macrophage inhibitor factor (MIF)
- Sex hormones (in women: testosterone, estradiol and estrone)
- Glucocorticoids
- Leptin
- Adiponectin
- Resistin
- Visfatin
- IL-6
- NO
- PPAR-γ
- Atrial natriuretic peptide (ANP)

- Cardiovascular and reologic effects, sleep apnea
- Renal effects
- Activation of the sympathetic nervous system
- Metabolic effects (dyslipidemia, carbohydrate intolerance)
- Endocrine effects (hyperinsulinism, insulin resistance, hypercortisolism, increased erythropoietin secretion)
- Increased coagulation/decreased fibrinolysis (↑PAI)
- Haematologic effects



Więcek A. et al., Nephrol. Dial. Transplant. 2002; 17; 194-195

Obesity and kidney

Pathogenic factors

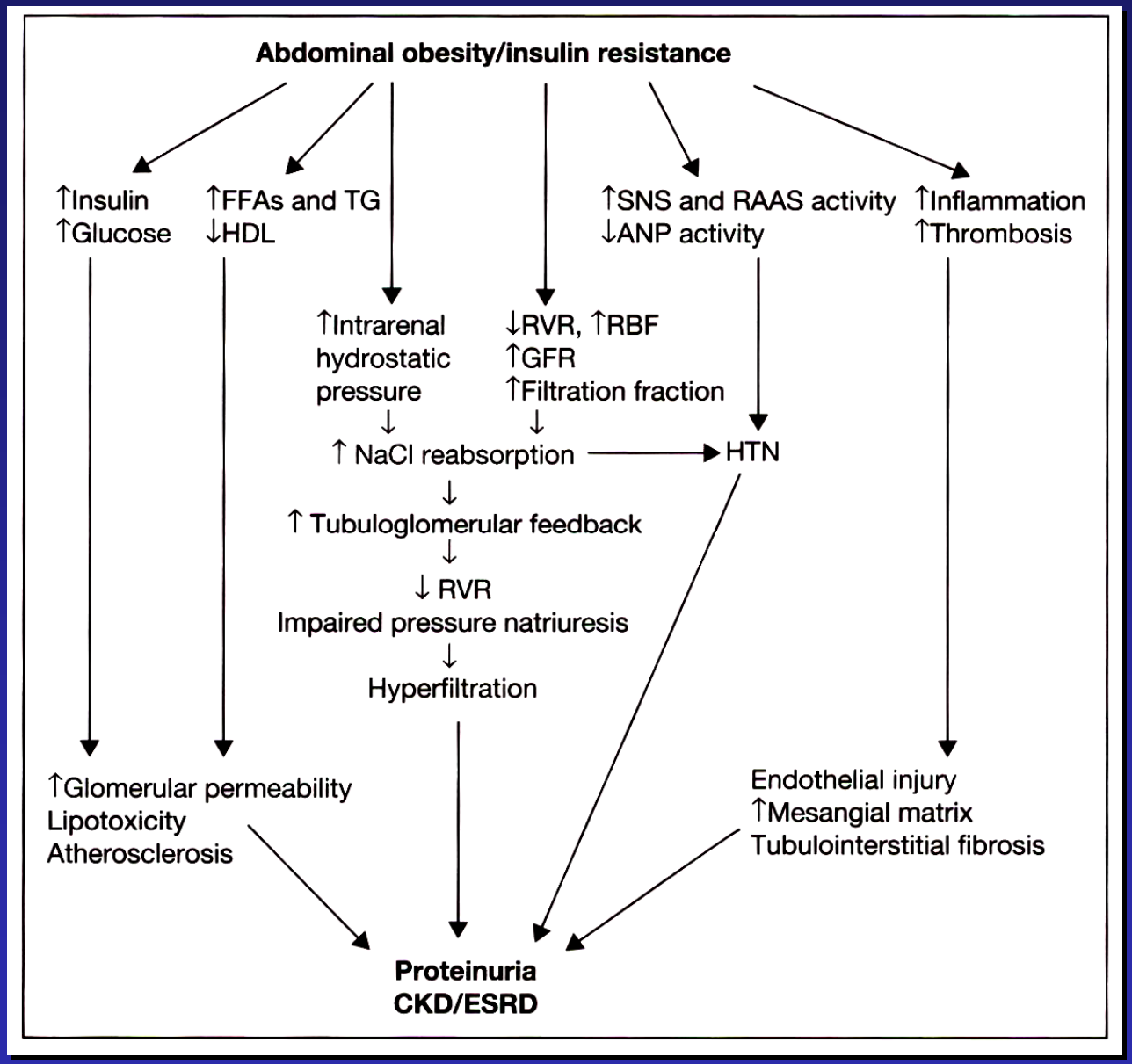
- Hypertension
- RAA and SNS activation
- Insulin resistance / diabetes mellitus
- Hyperlipidemia (mesangium proliferation)
- Hyperleptinemia
- Hypoadiponectinemia
- Increased abdominal pressure

Obesity and kidney

Pathogenic factors

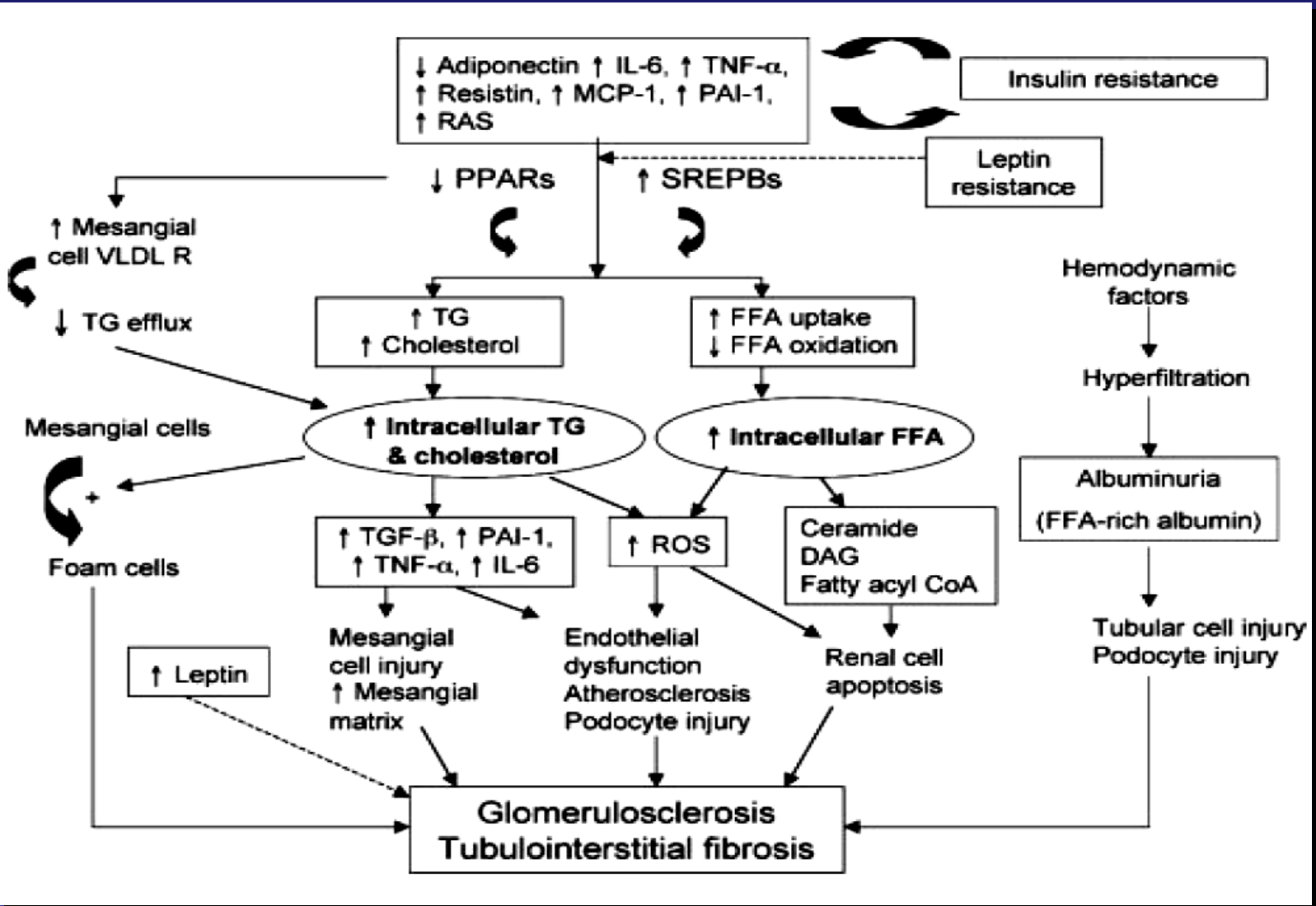
- Glomerular hyperfiltration
- Endothelial proliferation in glomeruli
- Increase TGF-β1 production by endothelial cells in glomeruli
- Overexpression TGF β receptors on mesangial cells
- Increase collagen type IV deposition in glomerular matrix
- Increase angiogenesis

Mechanism of kidney injury caused by obesity



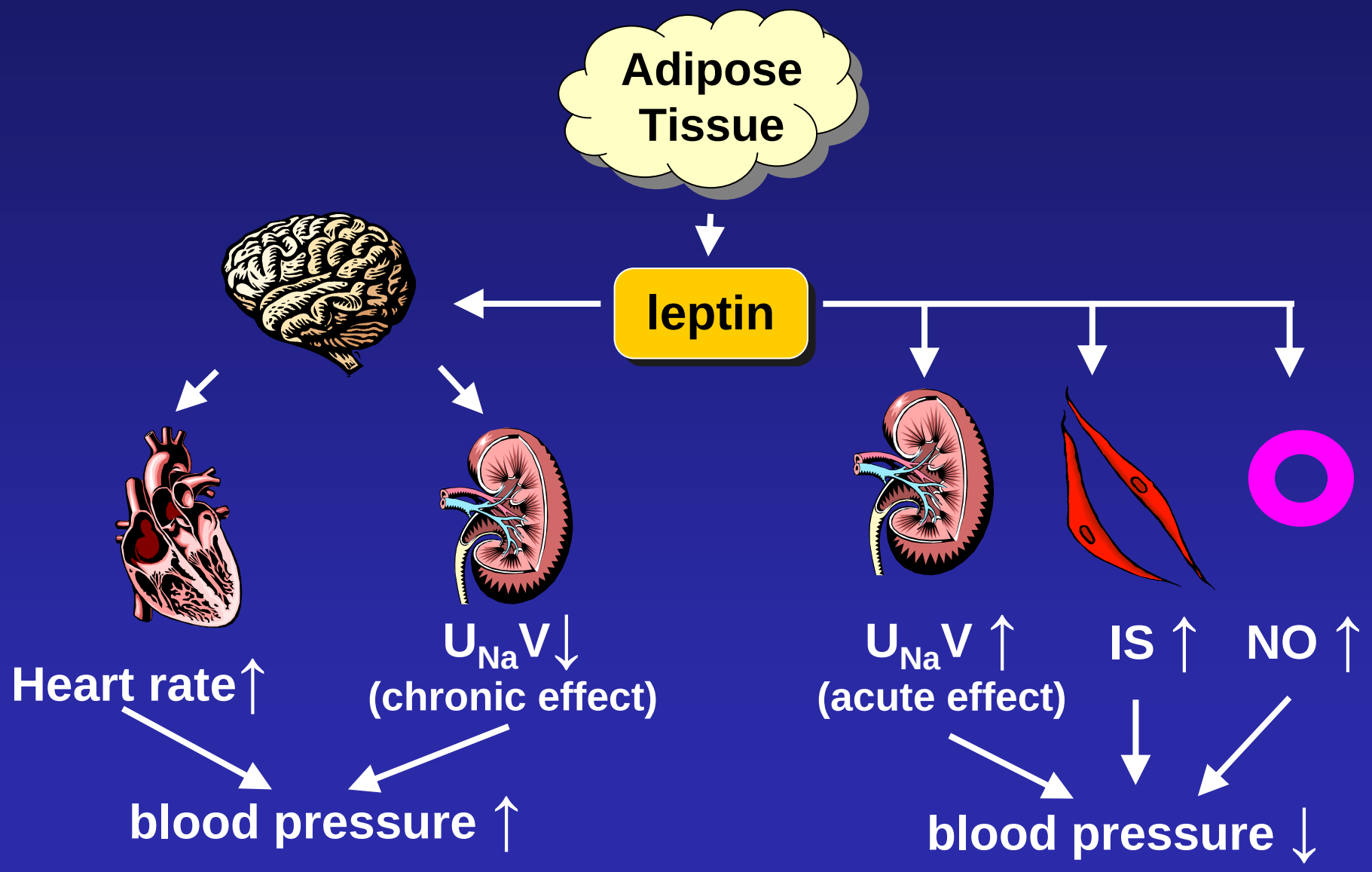
Thakur V et al. Contrib Nephrol, 2006:151

Potential mechanisms of renal dysfunction related to inflammatory cytokines and lipotoxicity in obesity and obesity initiated metabolic syndrome



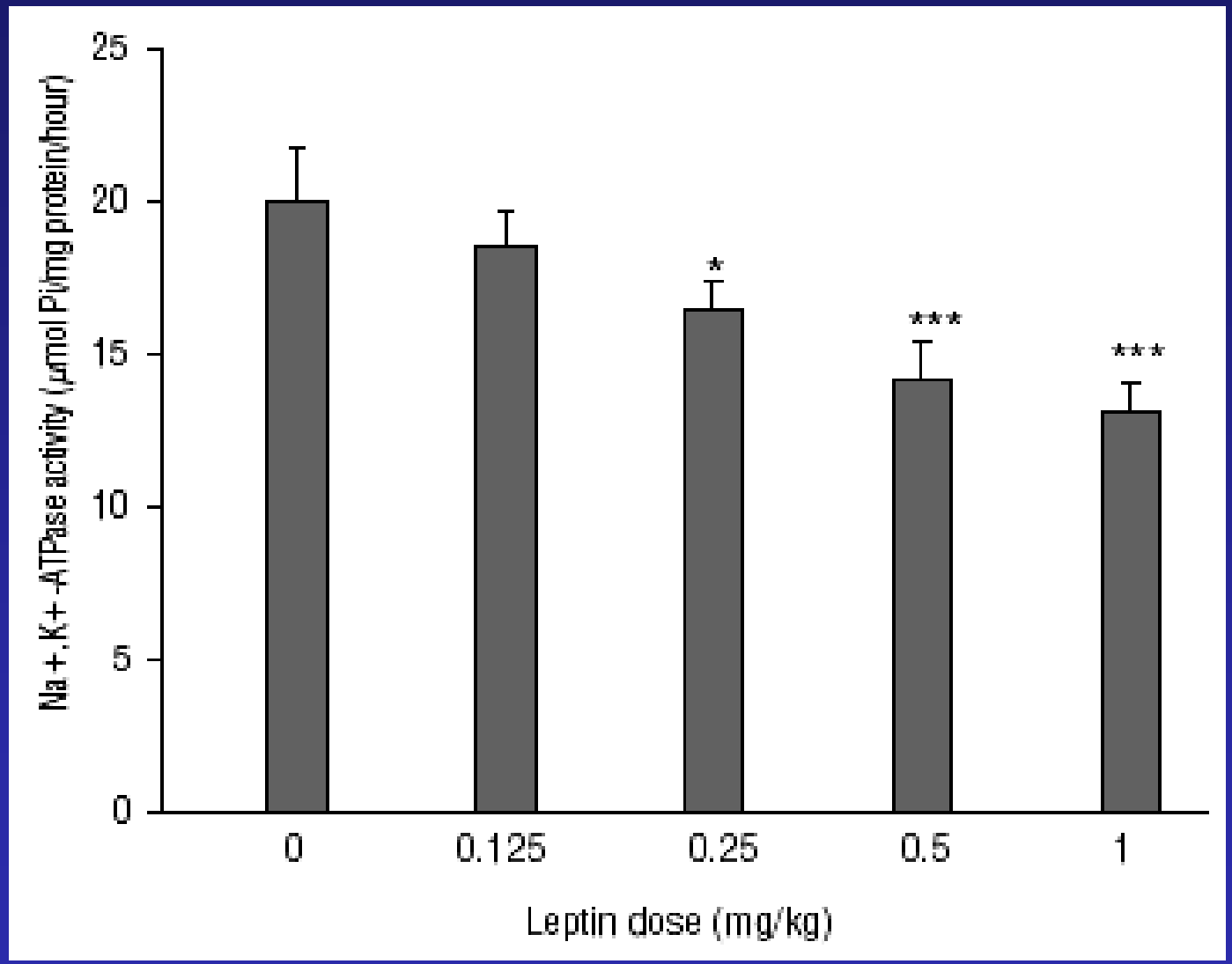
Wahba I.M. et al. Clin. J. Am. Soc. Nephrol., 2007; 2: 550-562

Cardiovascular and reanal effects of leptin



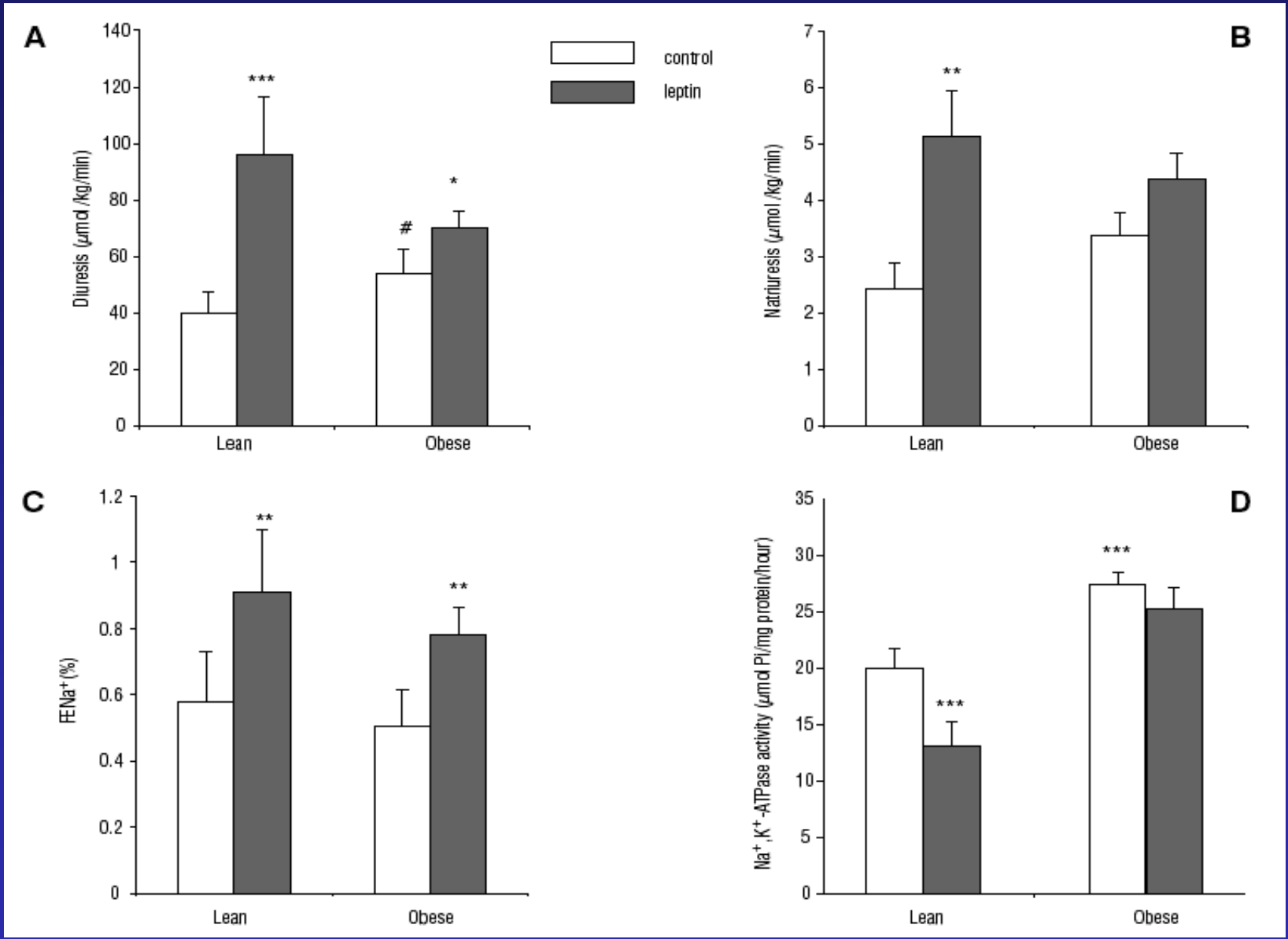
Engeli S. et al. Horm Metab Res, 2000; 32; 490

Na^+, K^+-ATPase activity increase in dose-depentet manner accoriding to leptin concentration in non-obese rat kidney



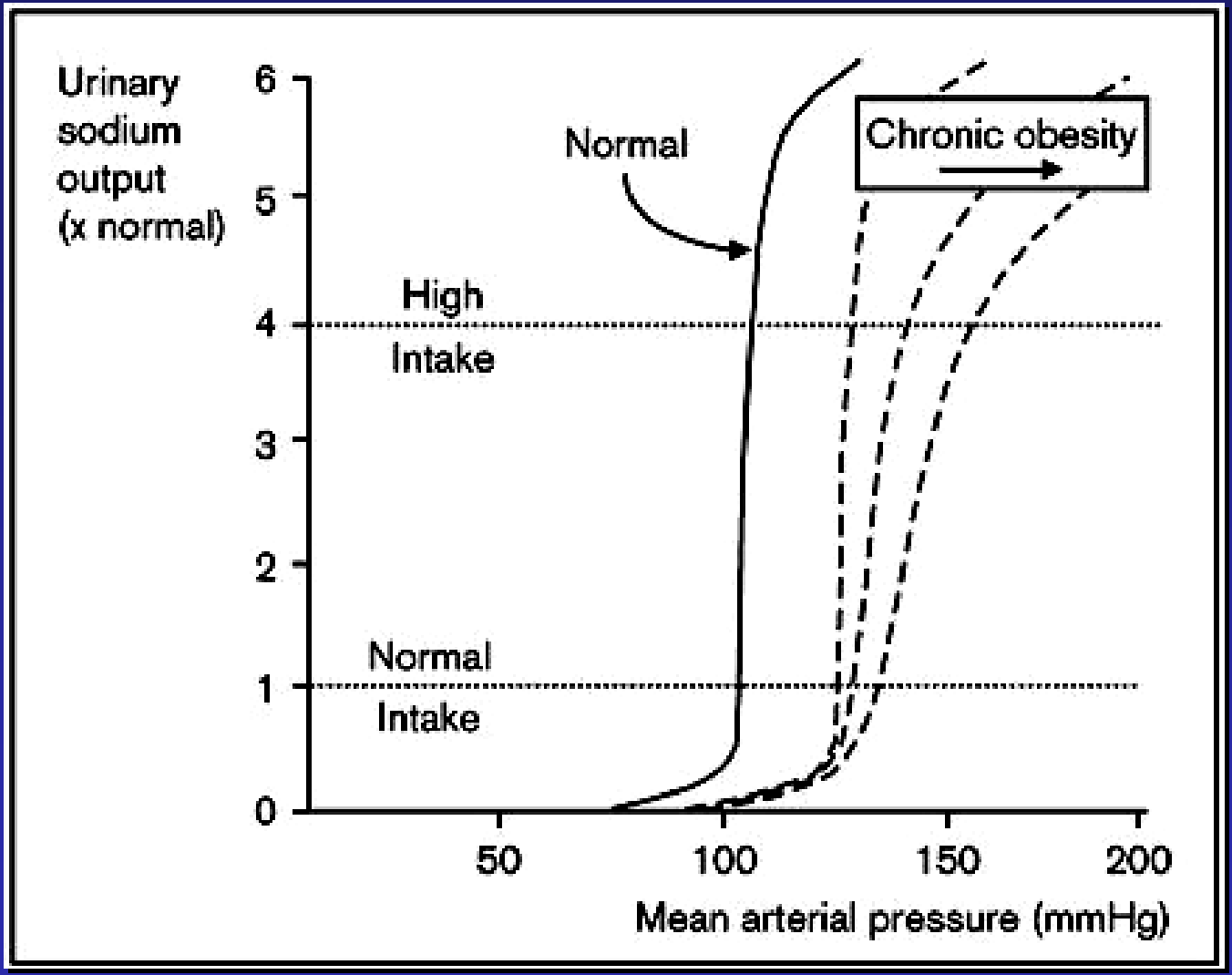
Bełtowski J. et al., Med Sci Monit, 2002; 8(6): BR221-229

Leptin effect on kidney function in obese and lean rats



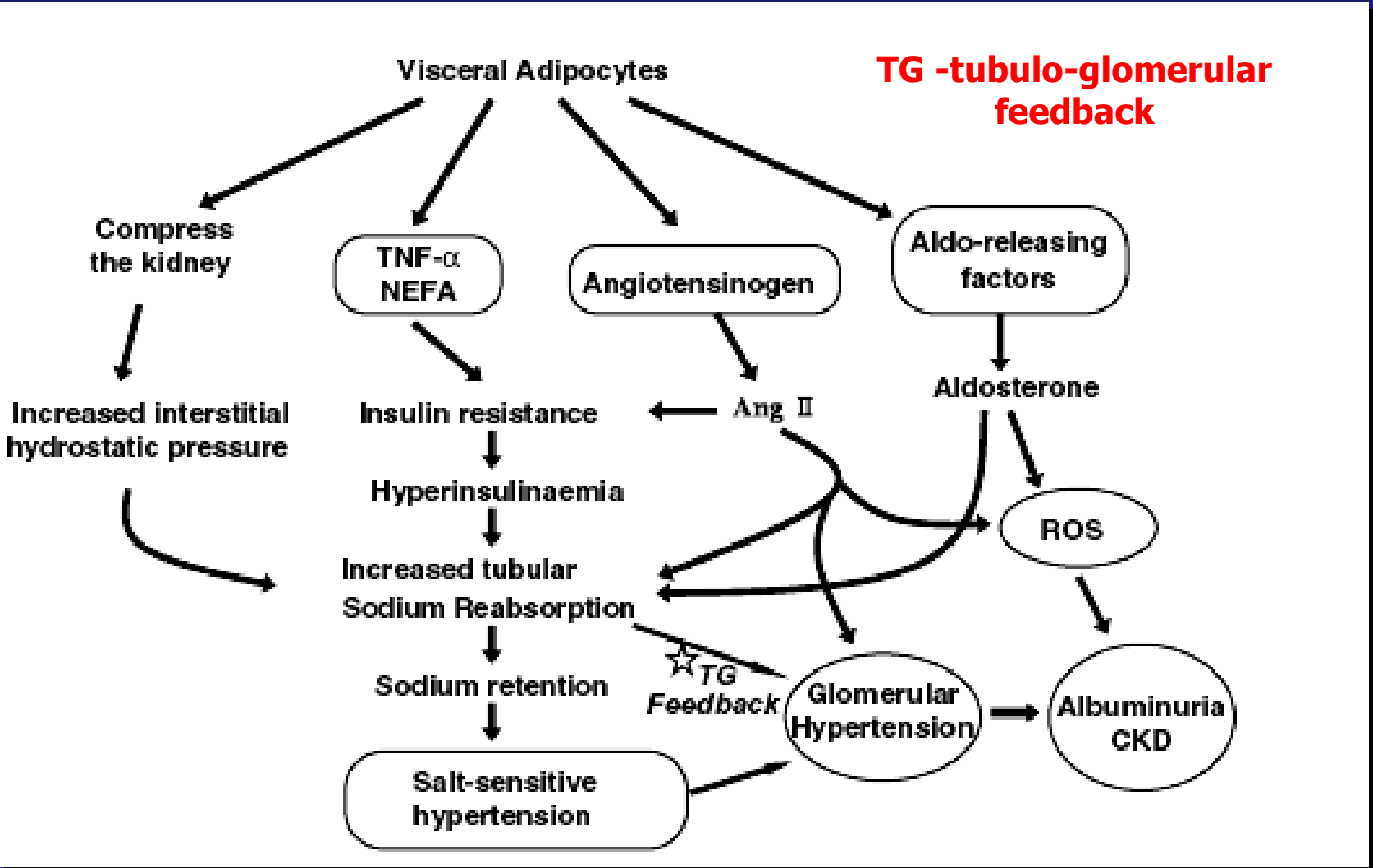
Bełtowski J. et al., Med Sci Monit, 2002; 8(6): BR221-229

Effect of obesity to shift renal pressure natriuresis curve to higher arterial pressure



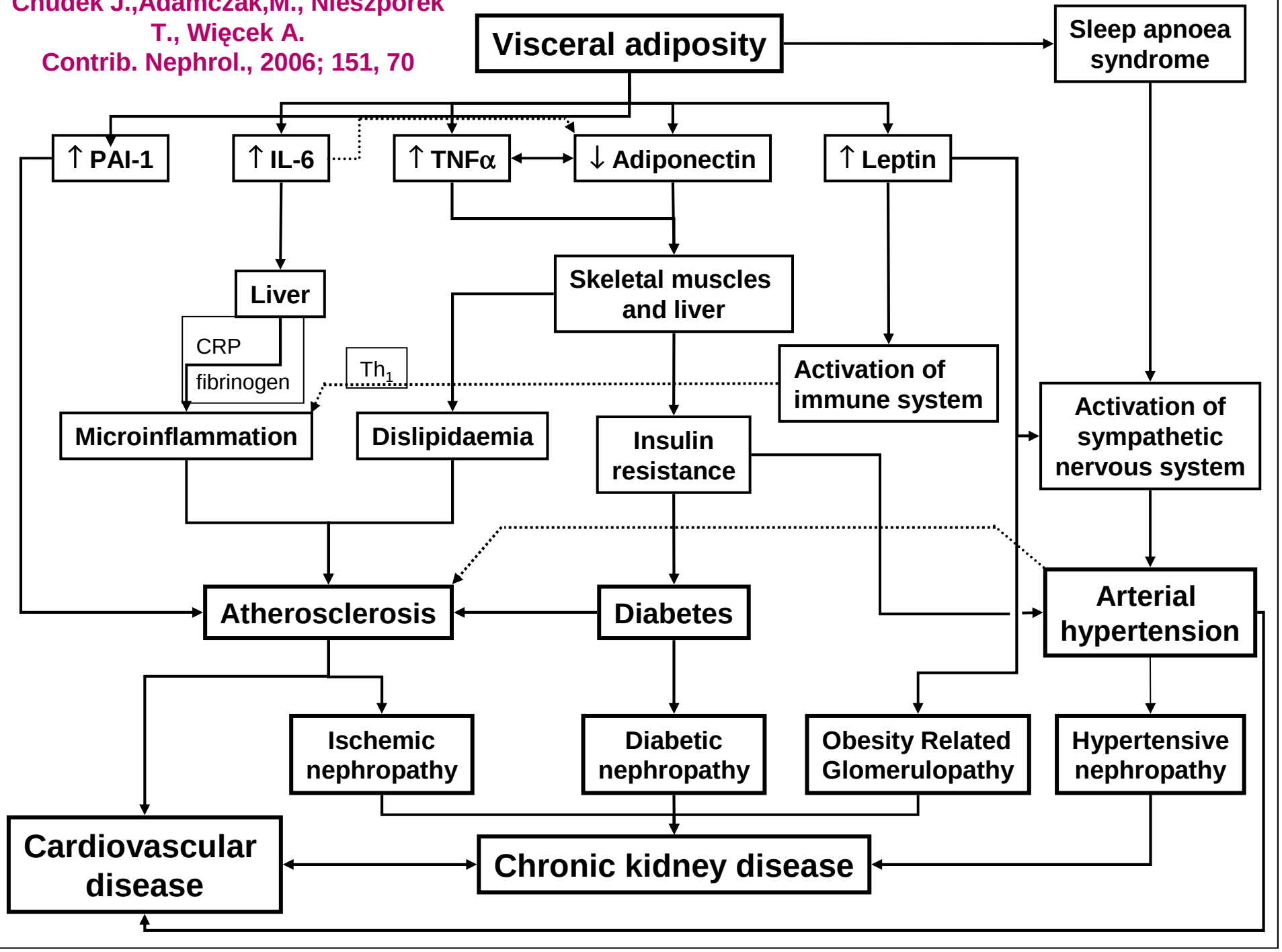
Hall J.E. et al. Curr Opin Nephrol Hypertens 2003, 12: 195-201

Possible mechanism underlying the development of salt-sensitive hypertension and CKD in metabolic syndrome

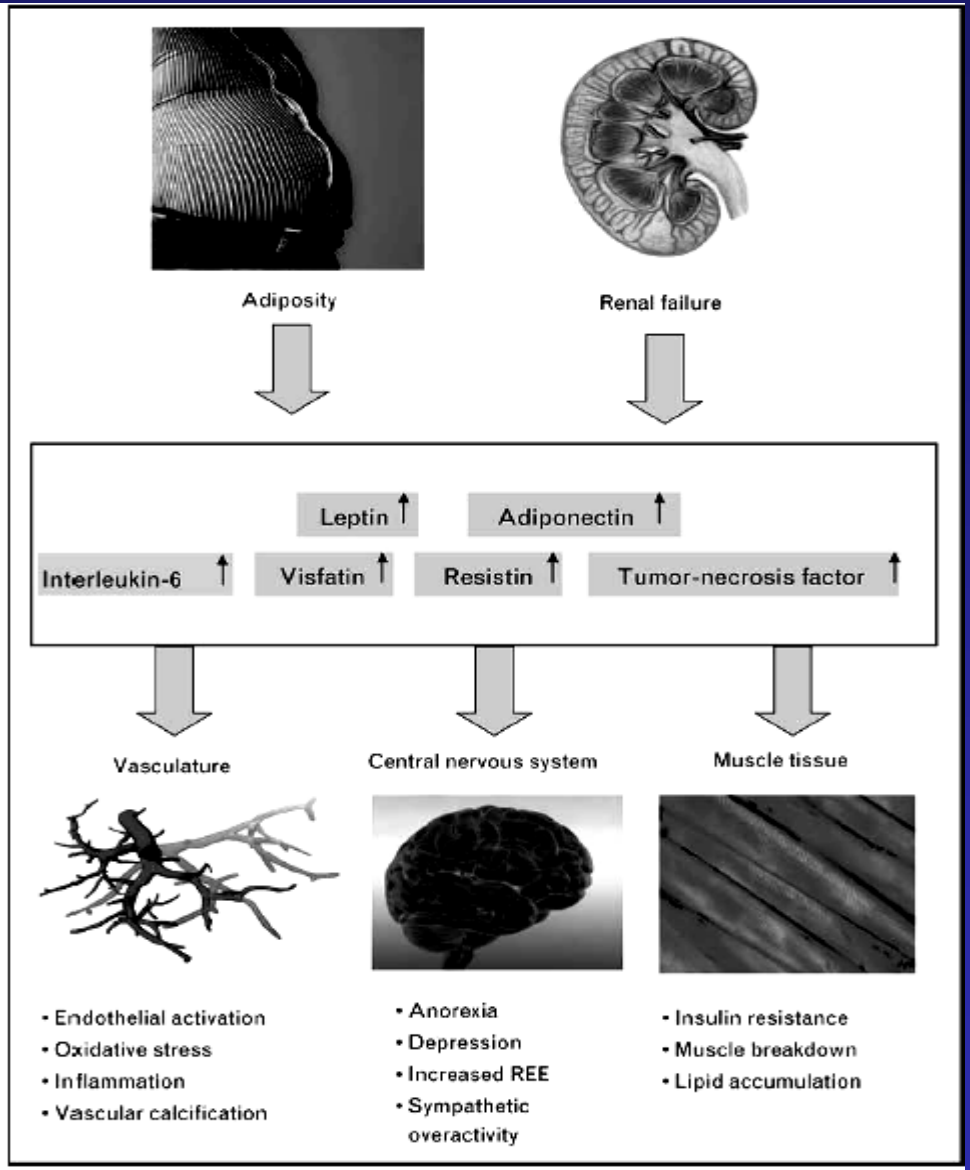


Fujita T. Nephrol. Dial. Transplant., 2007; 22: 3102-3107

Chudek J.,Adamczak,M., Nieszporek T., Więcek A.
Contrib. Nephrol., 2006; 151, 70



Obesity and impaired renal function increase adipokines concentration



Axelsson J, Stenvinkel P. Curr Opin Nephrol Hyperten 2008; 17: 25-31

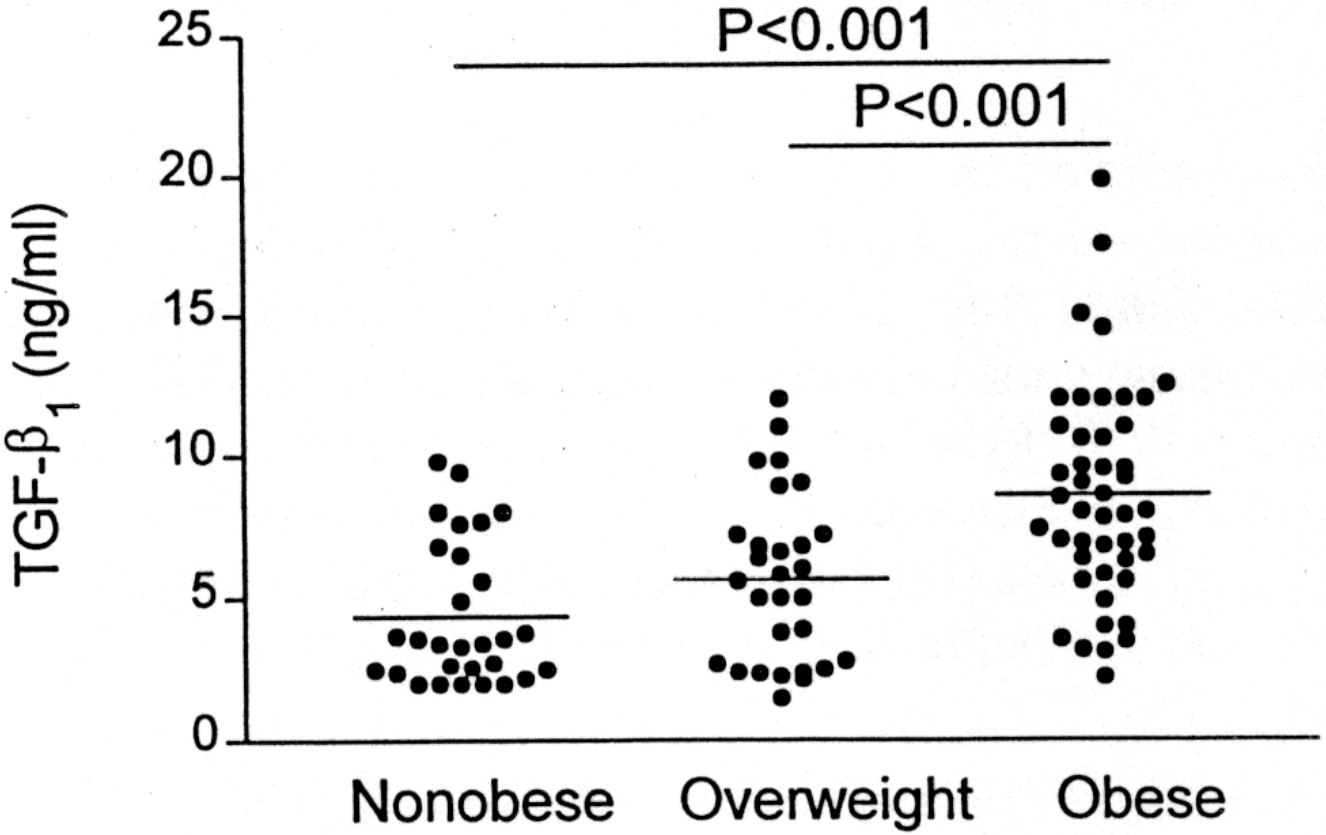
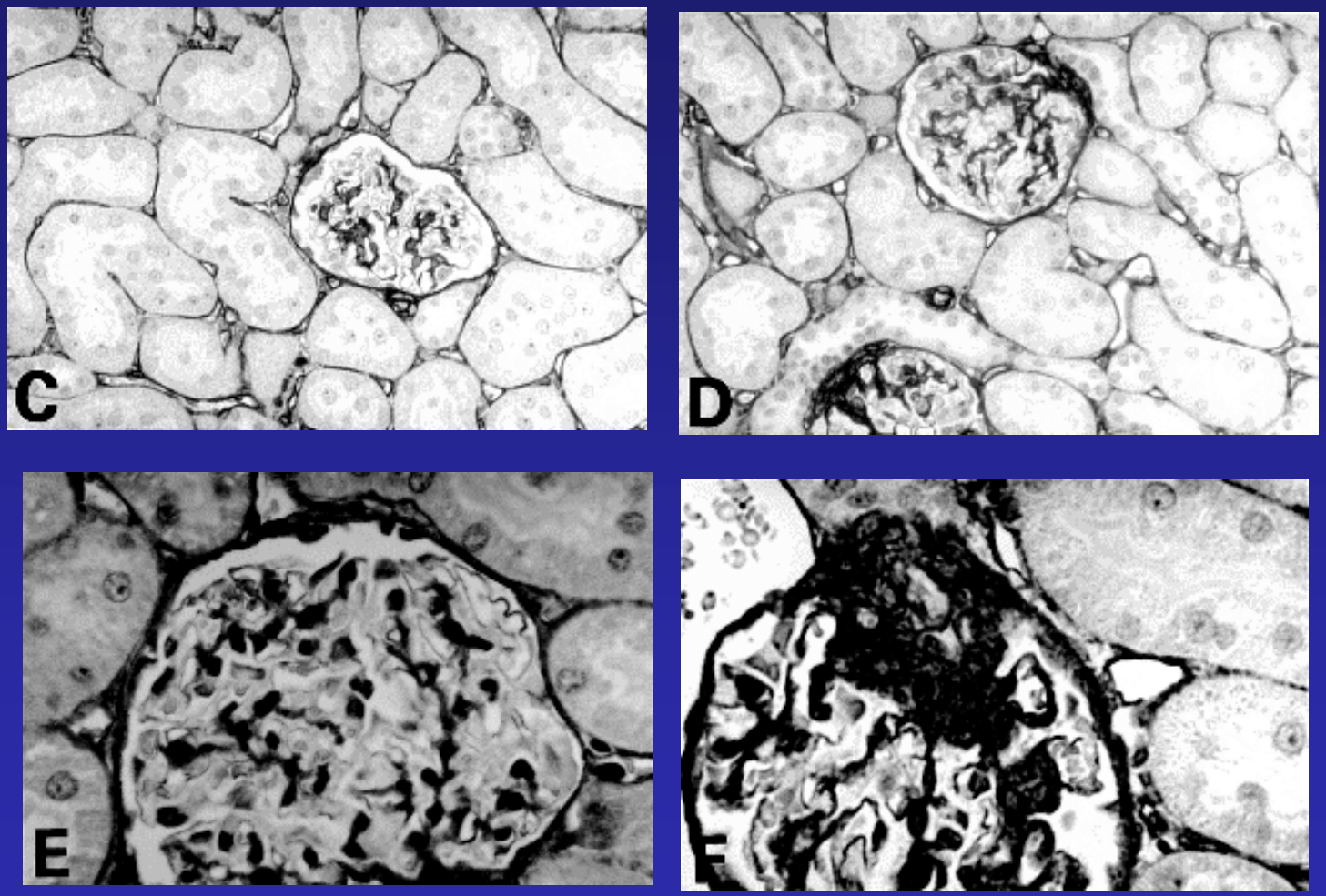


FIG. 1. Scatterplot of TGF-β_1 plasma levels in nonobese (n = 29), overweight (n = 29), and obese (n = 46) hypertensive patients. TGF-β_1 = transforming growth factor-β_1.

Porreca E. et al.: Am. J. Hypertens., 2002, 15: 759-765

Staining for collagen type IV in rats infused for three weeks with solvent (C,E) or leptin (D,F).

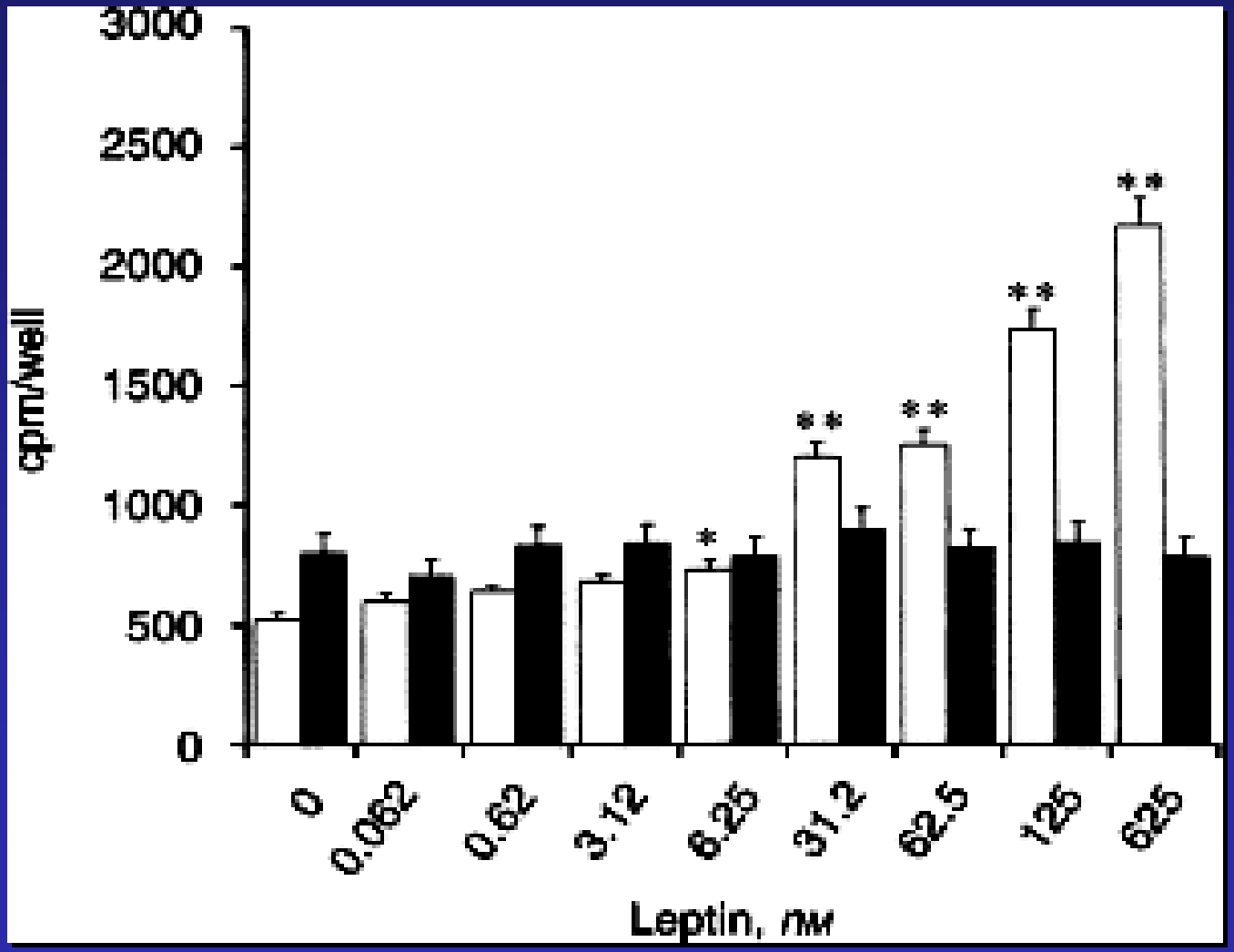


Wolf G. et al. Kidney Int 1999, 56: 860-872

Leptin-induced proliferation

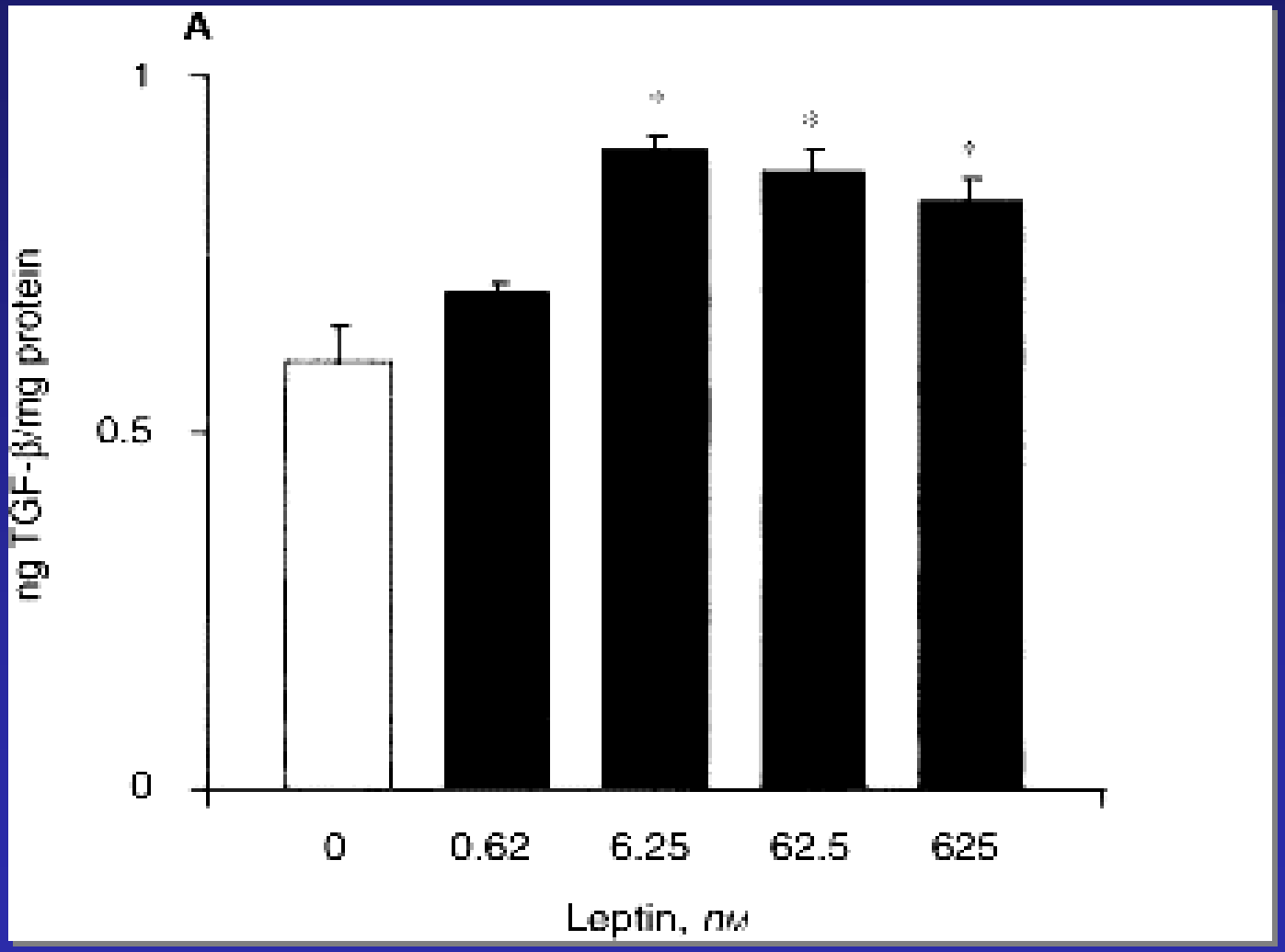
(□) Glomerular Endothelial Cells; (■) mesangial cells;

****P< 0.05; **P< 0.01 vs. unstimulated controls**



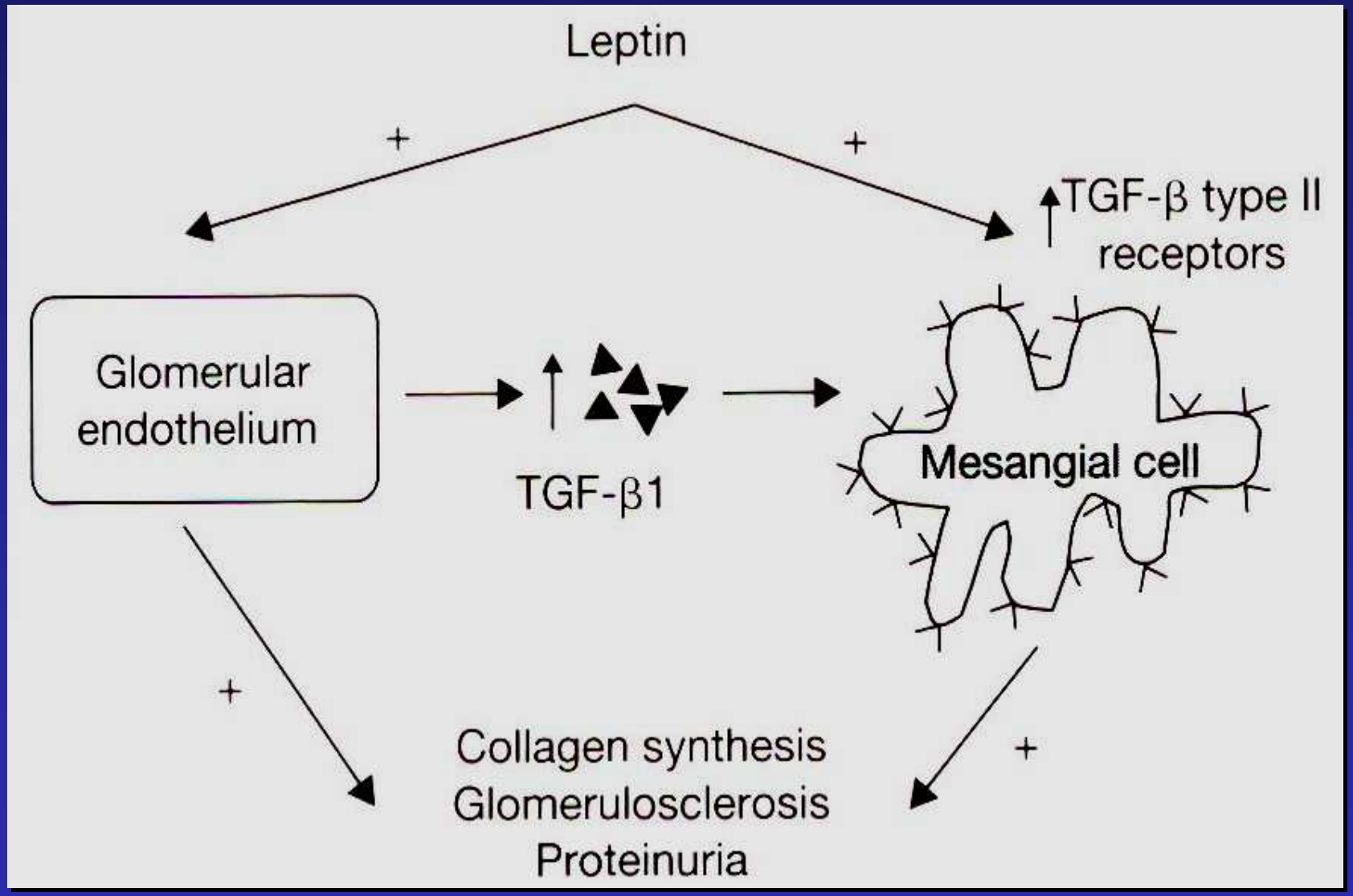
Wolf G. et al. Kidney Int 1999, 56: 860-872

Leptine increase TGF- β1 expression in endothelial glomerular cells



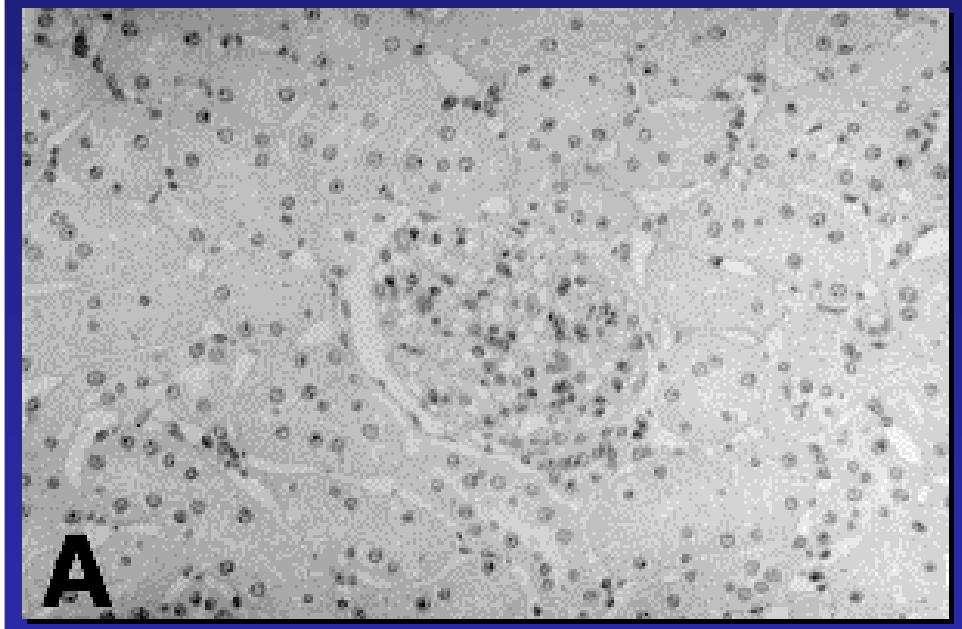
Wolf G. et. al. Kidney Int. 1999, 56, 860-872

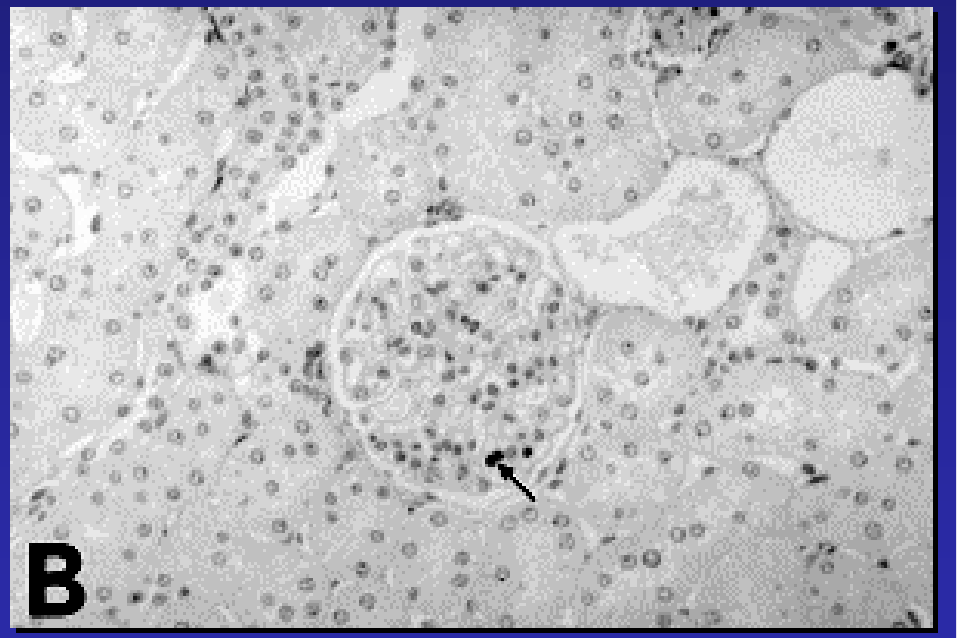
Leptin and renal fibrosis



Wolf and Ziyadeh. Contribution to Nephrology 2006:151

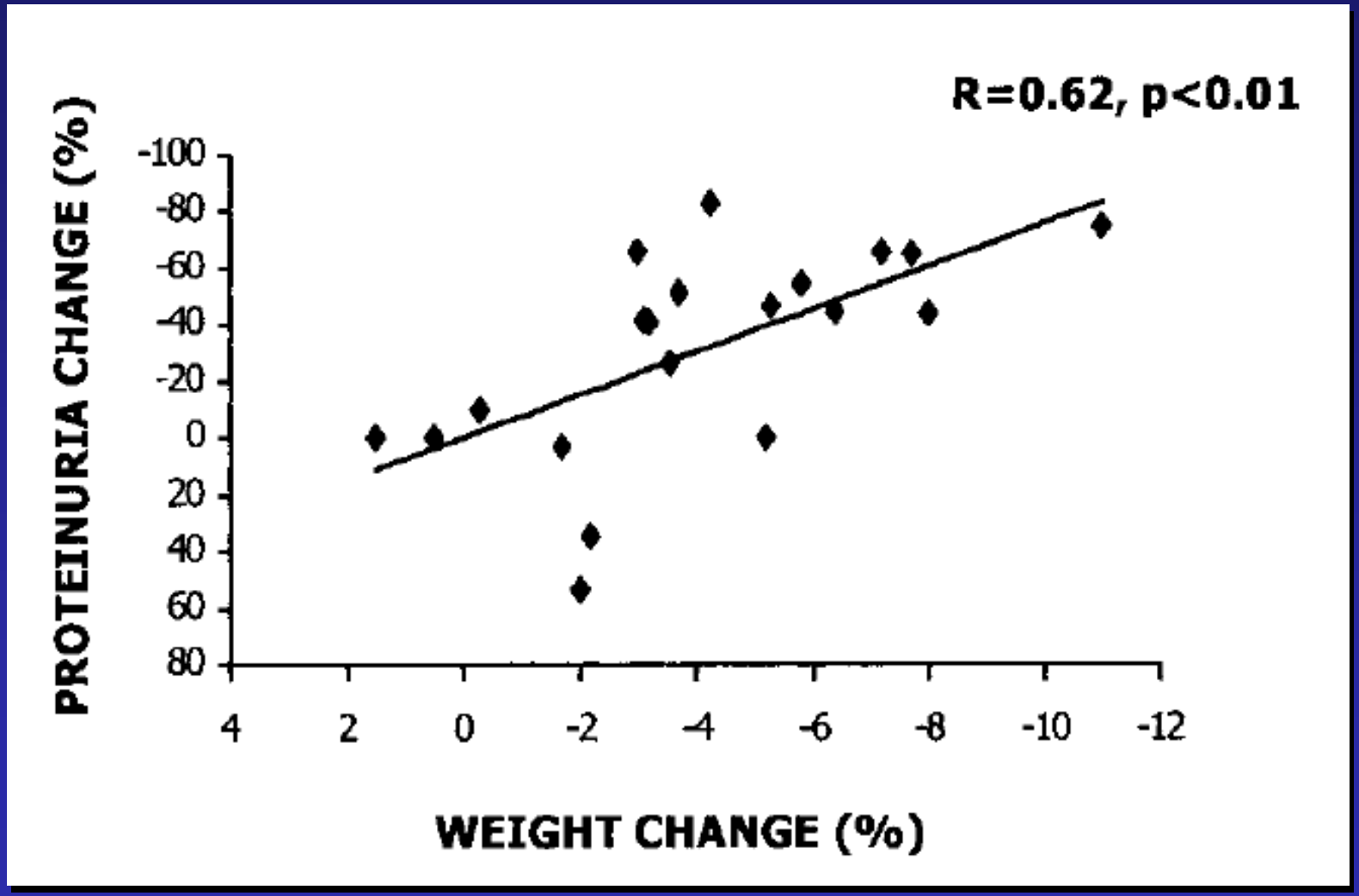
Kidney section of rats infused with solvent for 72 hours revealed no glomerular PCNA staining, suggesting very low basal proliferation in normal glomeruli (A). In contrast, in leptin-infused animals PCNA-expressing cells are found in glomeruli (arrow; B)





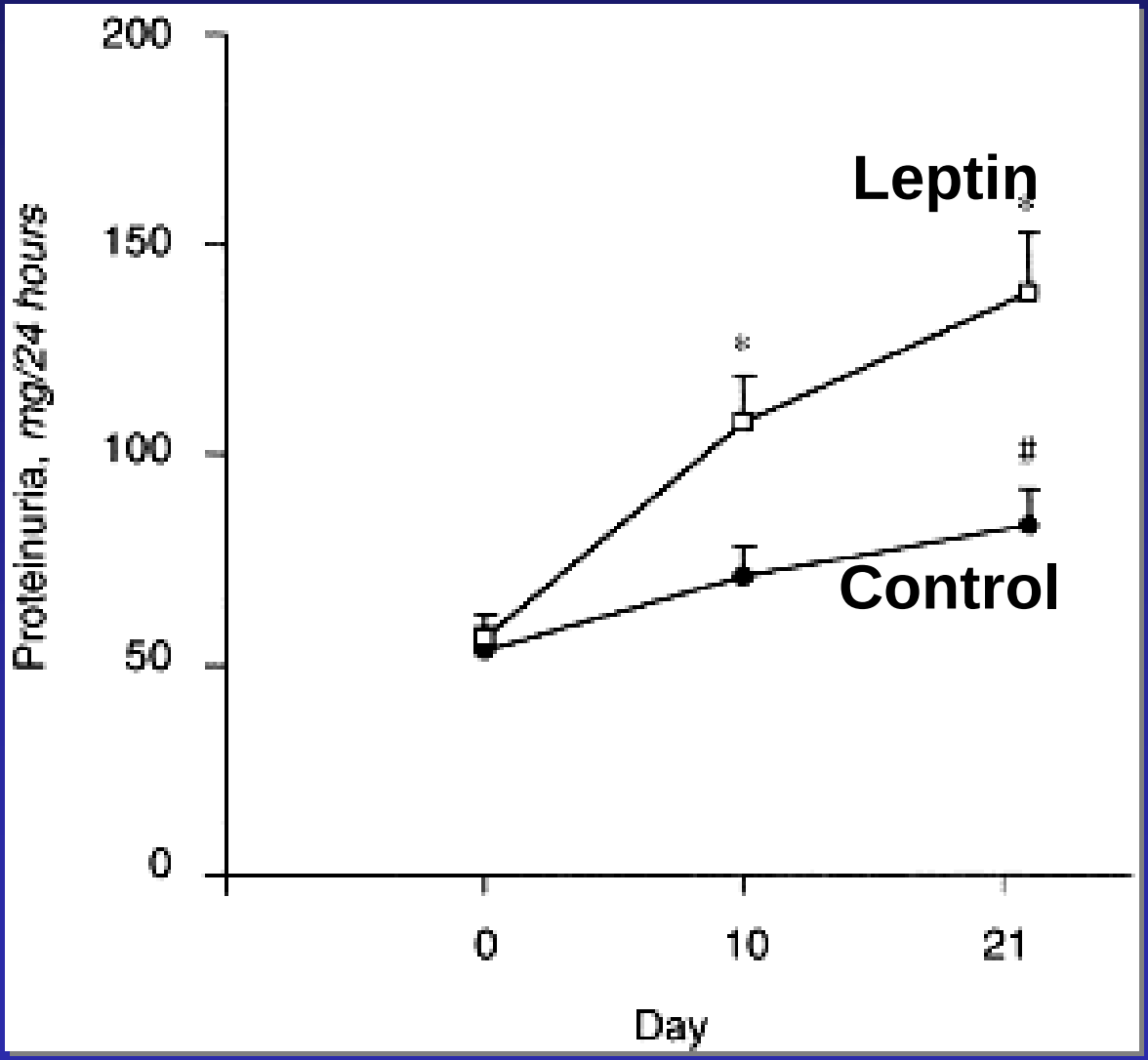
Wolf G. et al. Kidney Int 1999, 56: 860-872

Relationship of proteinuria and weight changes in diet-group patients



Morales E. et al., Am. J. Kidney Dis., 2003, 41: 319-327

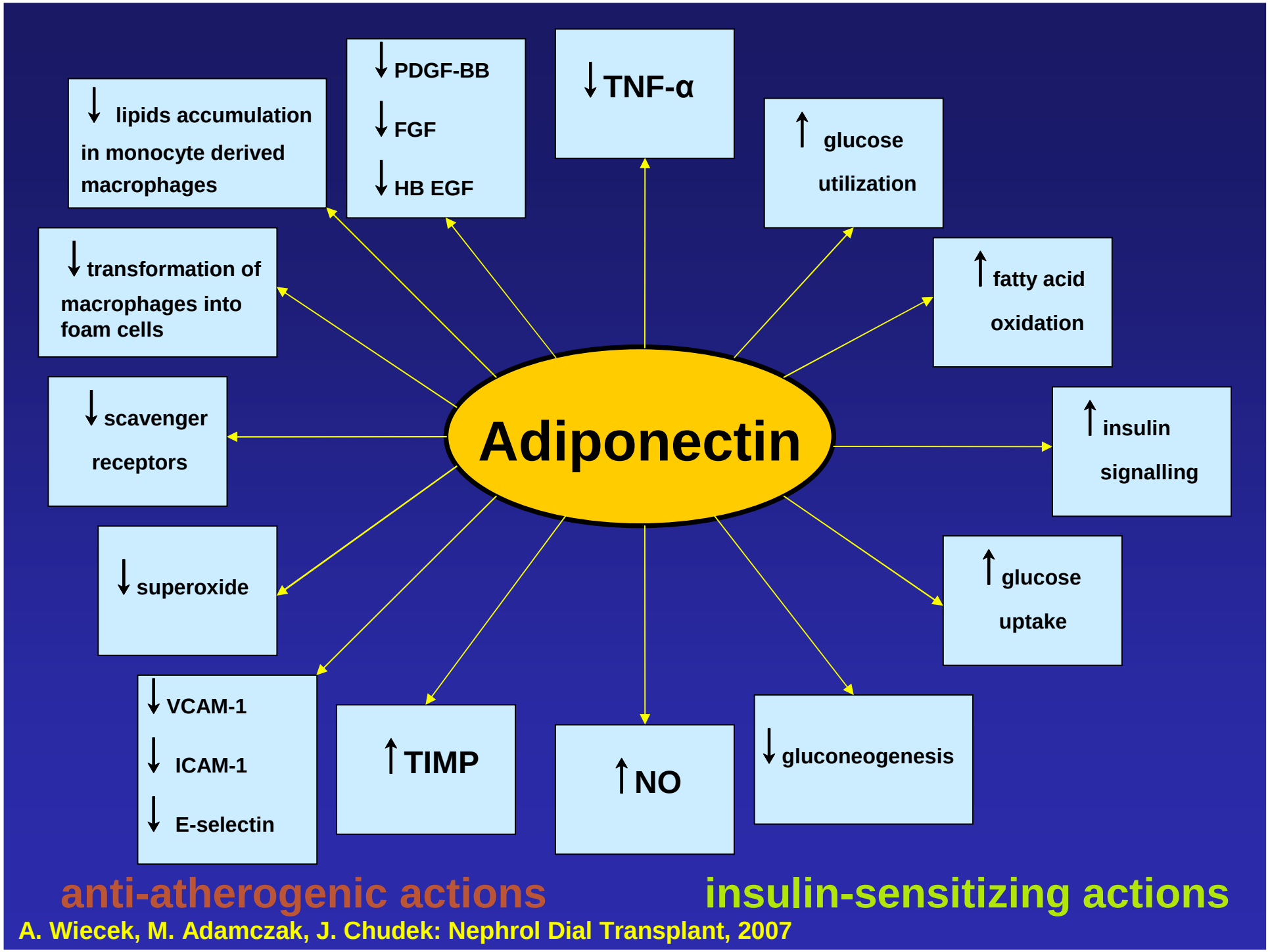
Leptin induced proteinuria –effect of 3 weeks leptin infusion



Wolf G. et. al., Kidney Int., 1999, 56, 860-872

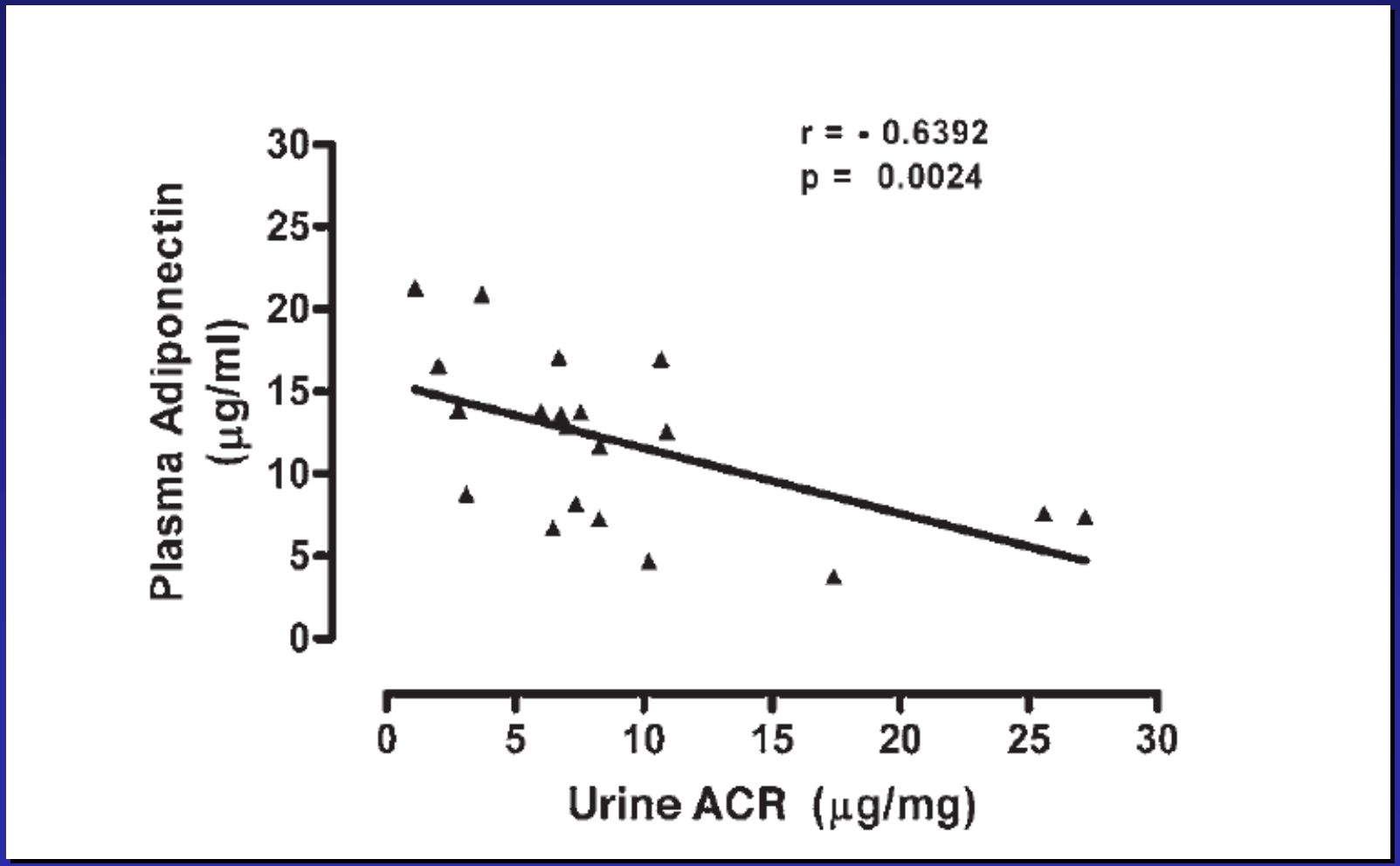
- Adponectin serum concentration and mRNA expression are decreased in:
  - Obese
  - Diabetes mellitus
  - Hypertension
  - Coronary artery disease
- PPRγ activators, ACEi, ARBs, rilmenidine, ribonabant – increase adponectin serum concentration and mRNA expression

Maeda N. et al., Diabetes, 2001, 50, 2094-2099



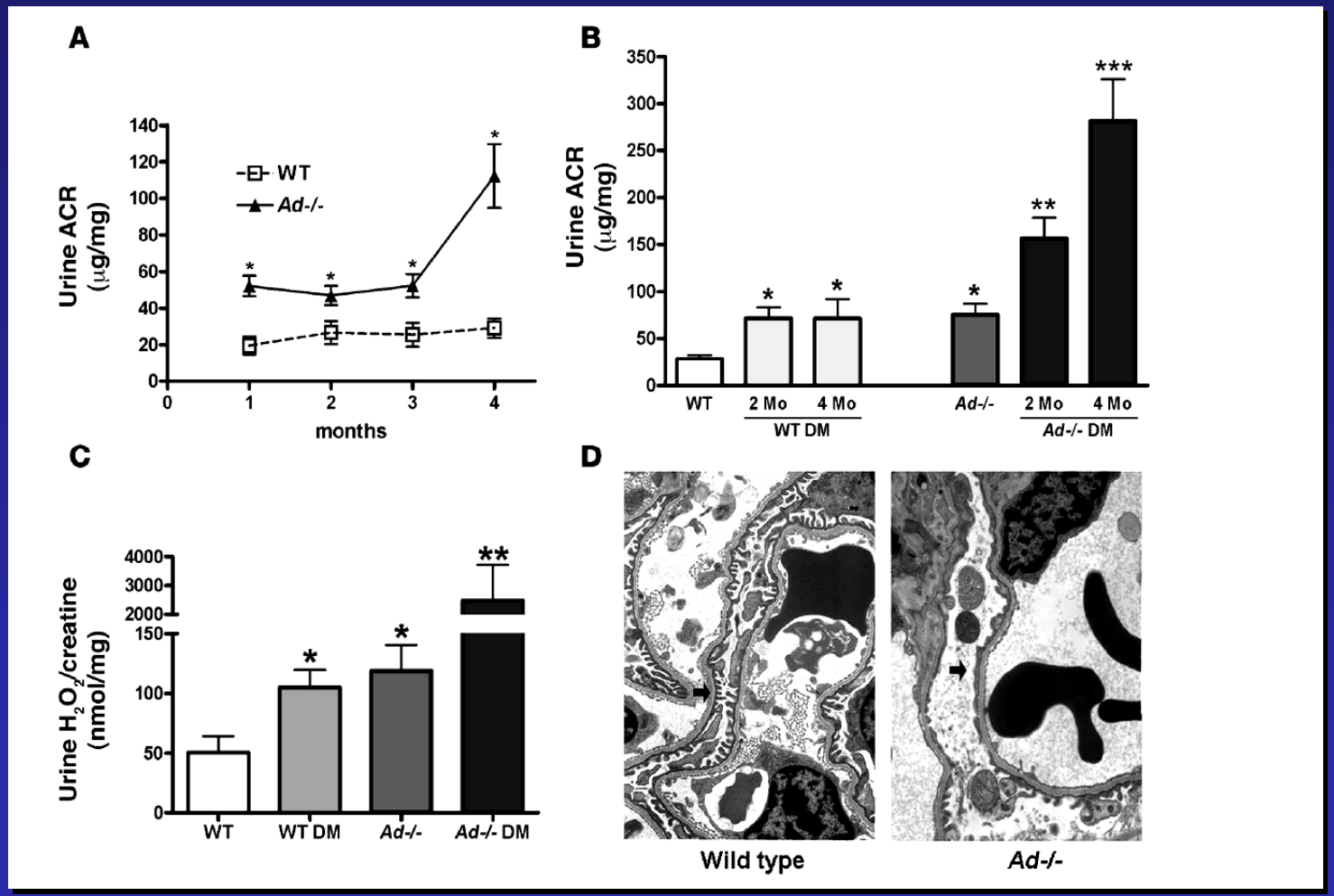
A. Wiecek, M. Adamczak, J. Chudek: Nephrol Dial Transplant, 2007

Negative correlation between albuminuria and plasma adiponectin levels in obese adults African Americans.



Sharama K J. Clin. Invest. 118:1645–1656 (2008)

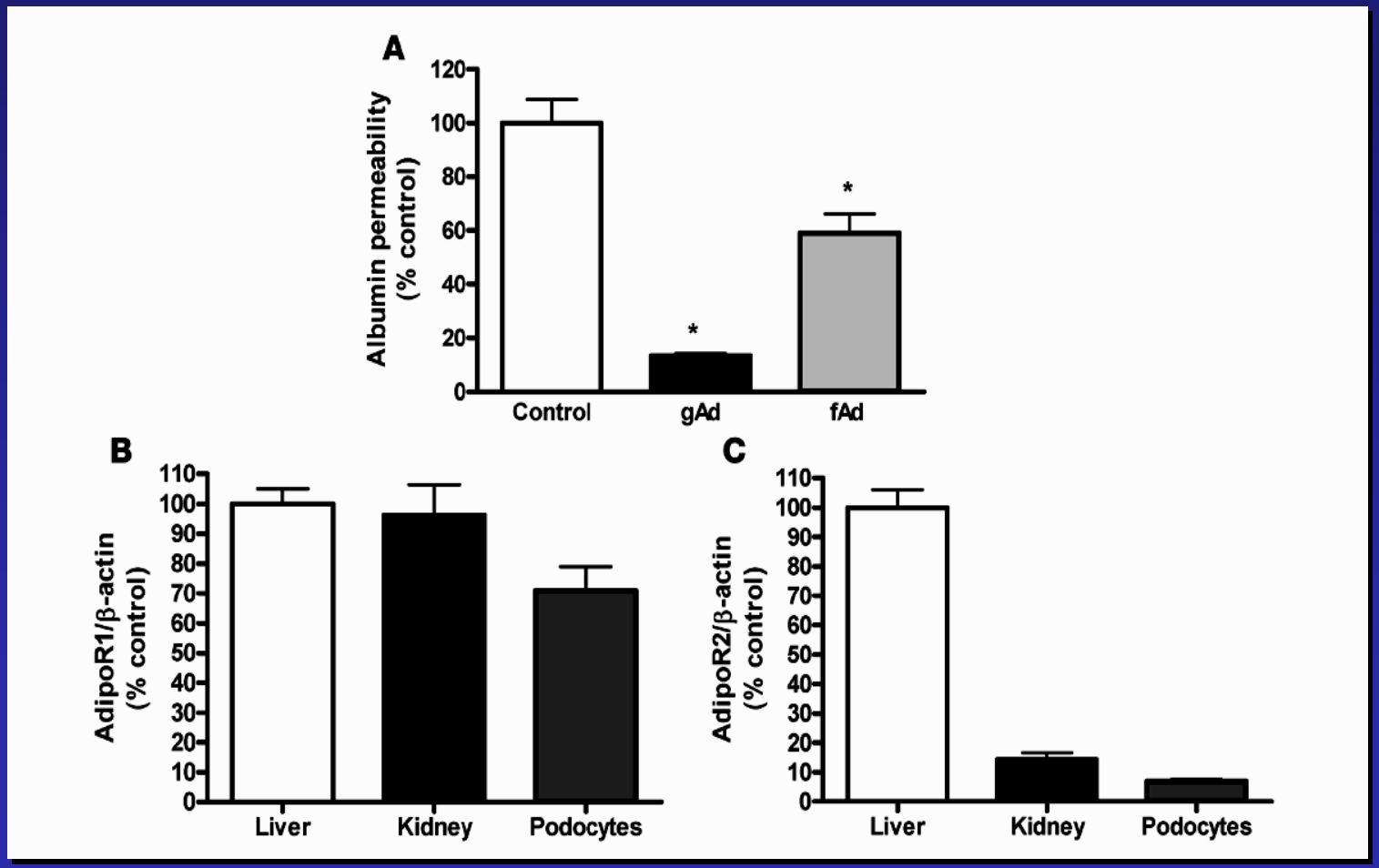
Ad–/– mice exhibit increased albuminuria, oxidant stress, and podocyte dysfunction



Sharama K J. Clin. Invest. 118:1645–1656 (2008)

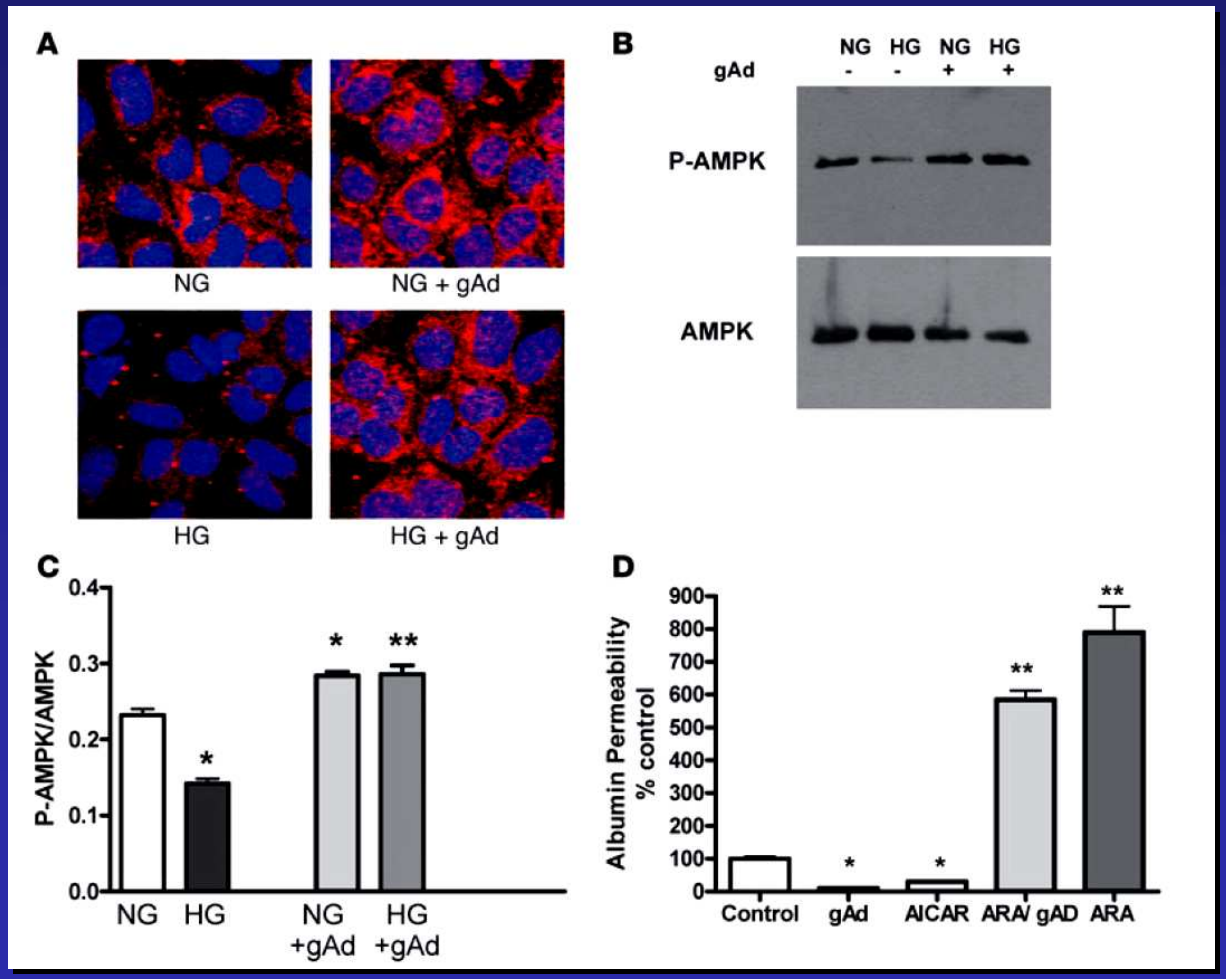
Adiponectin inhibits permeability across a podocyte monolayer

Direct action of adiponectin on podocytes independent of the systemic and/or metabolic effects of adiponectin



Sharama K J. Clin. Invest. 118:1645–1656 (2008)

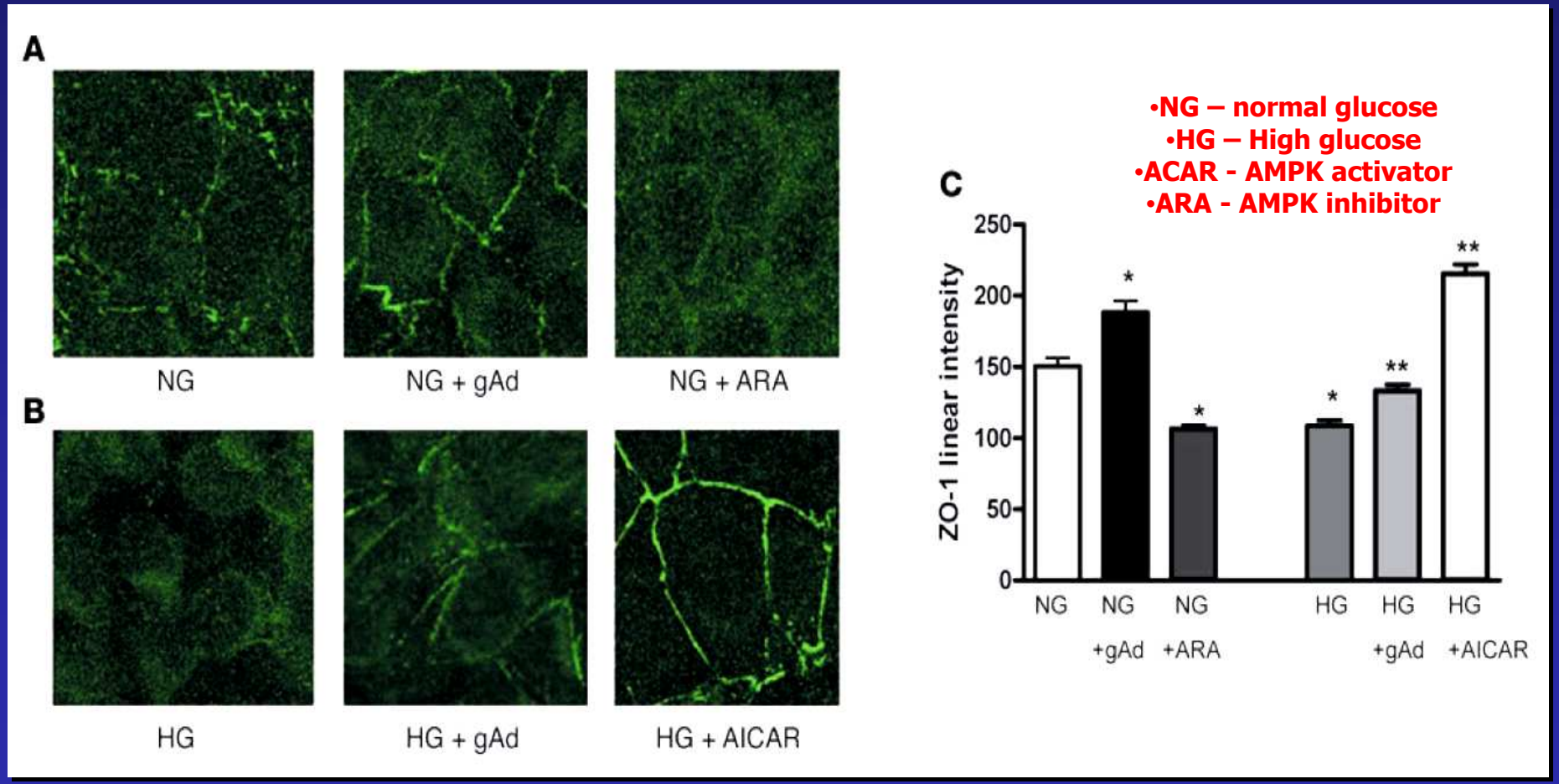
AMPK activity is increased by adiponectin and regulates podocyte permeability



- NG – normal glucose
- HG – High glucose
- ACAR - AMPK activator
- ARA - AMPK inhibitor

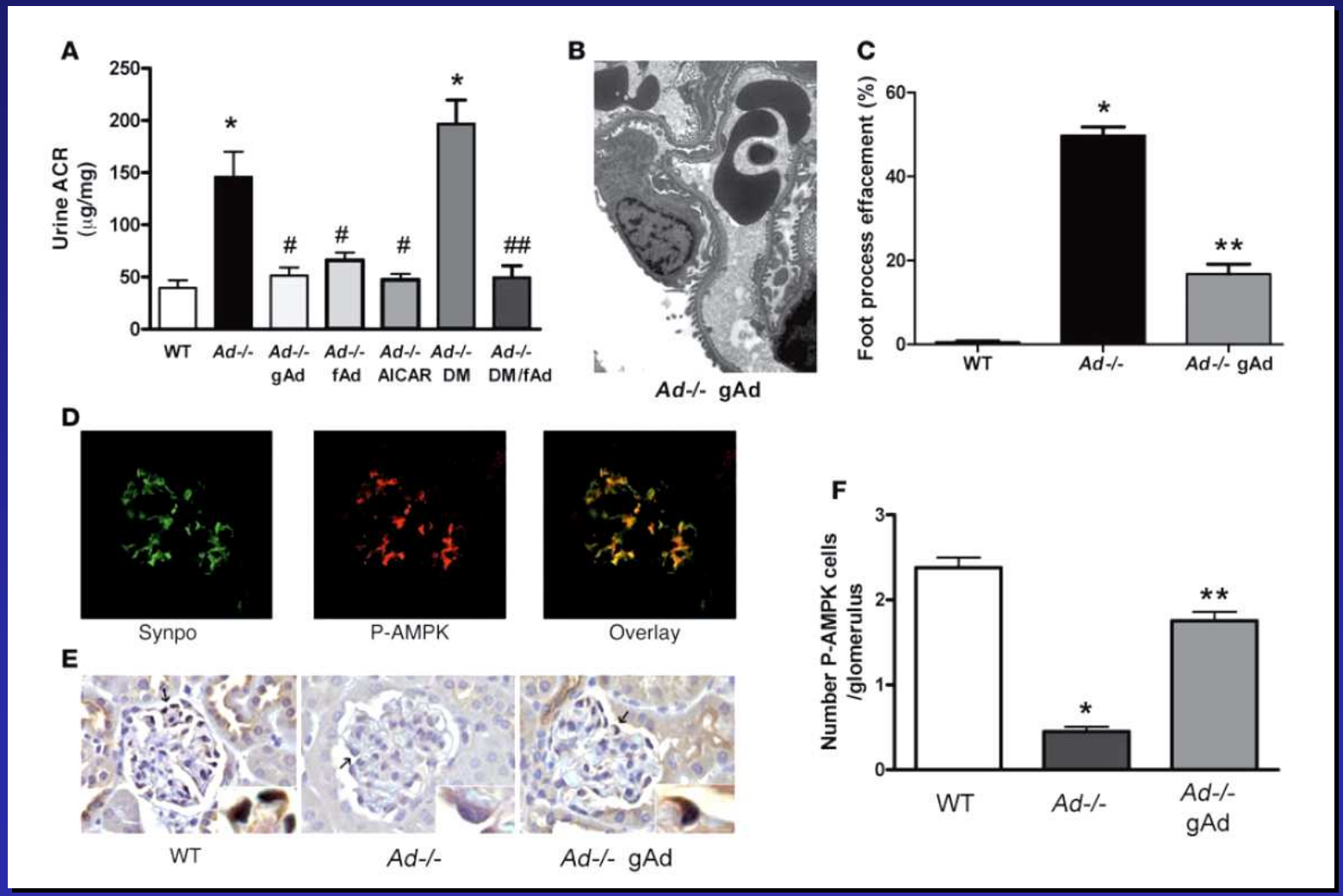
Sharama K J. Clin. Invest. 118:1645–1656 (2008)

ZO-1 (tight junction protein) localization is regulated by adiponectin and AMPK in podocytes



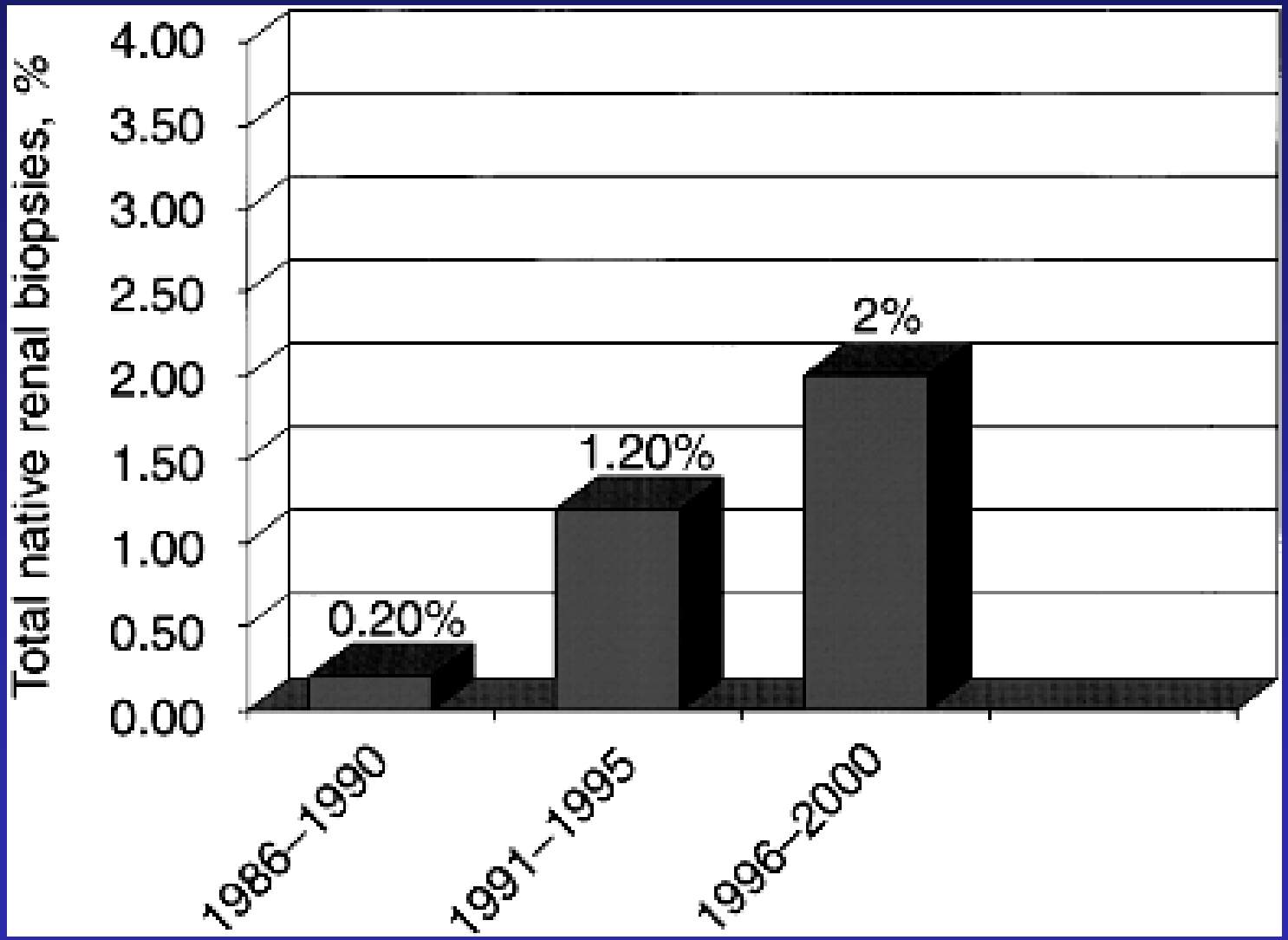
Sharama K J. Clin. Invest. 118:1645–1656 (2008)

Adiponectin restores normoalbuminuria and increases AMPK activity



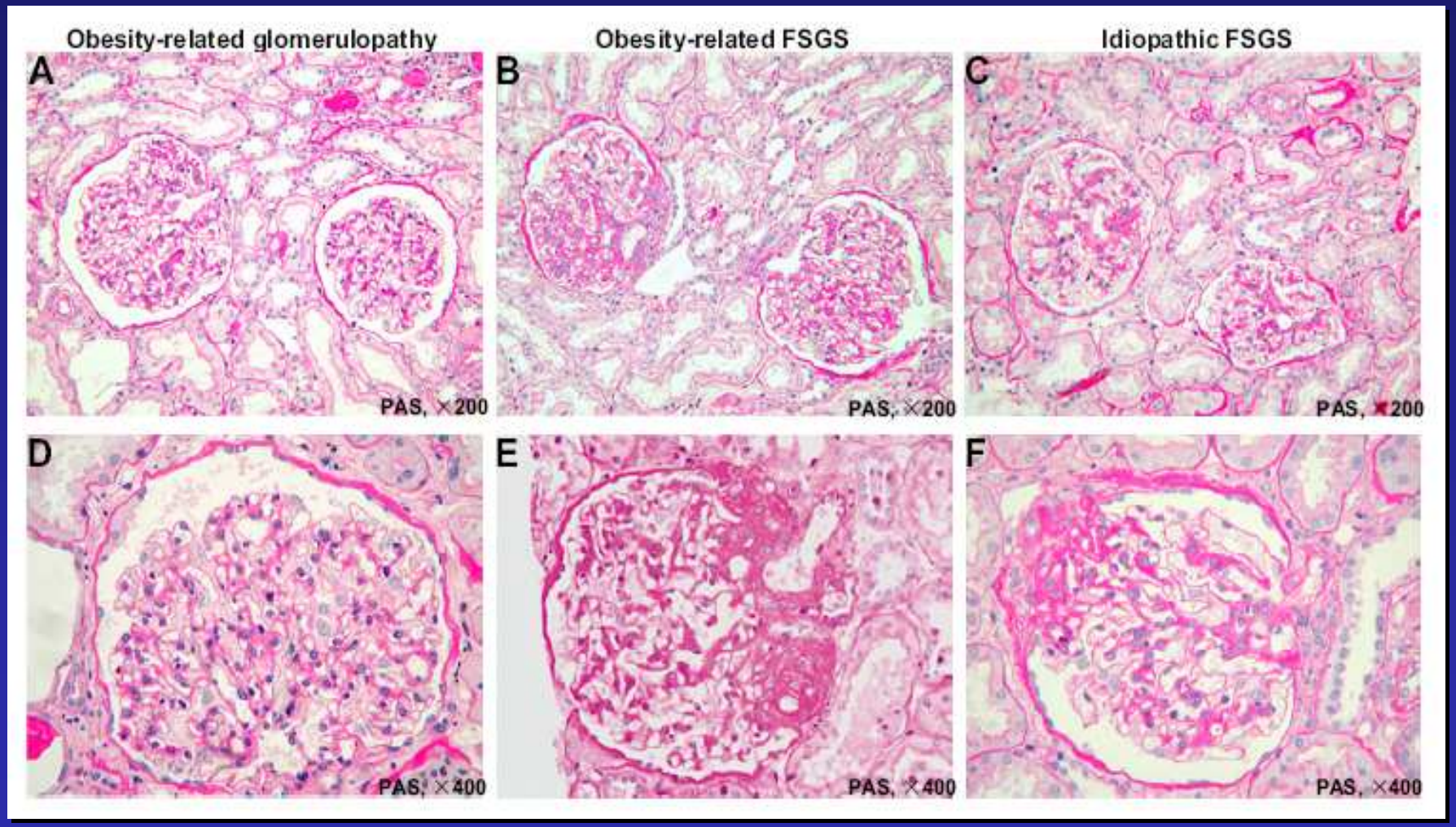
Sharama K J. Clin. Invest. 118:1645–1656 (2008)

The increased incidence of obesity-related glomerulopathy (ORG) is plotted as a percentage of total native renal biopsies received over a 15-year period.



Kambham N. et al., Kidney Int., 2001, 59, 1498-1509

Obesity-Related Glomerulopathy

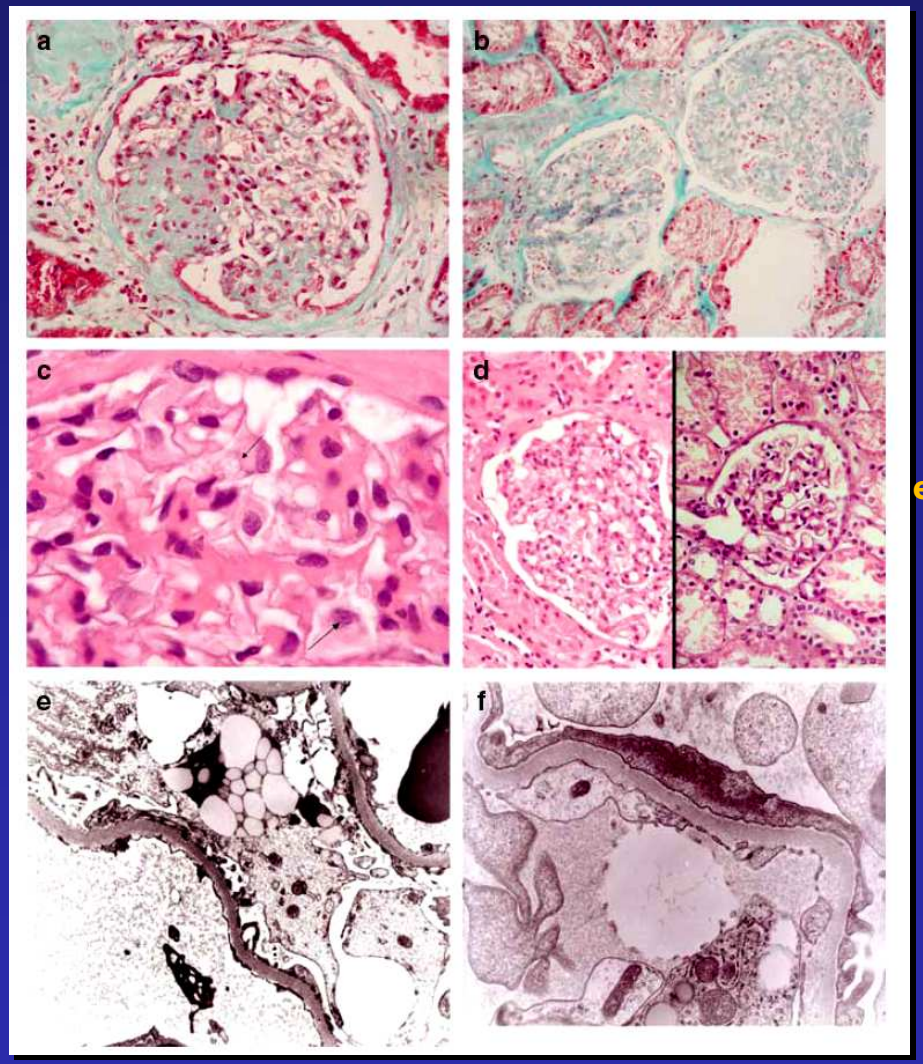


Chen HM et al. Am J Kidney Dis 52:58-65. 2008

Obesity-Related Glomerulopathy

Focal and segmental glomerulosclerosis

Global mesangial matrix increase in both glomeruli



Hypertrophic podocytes that contain intracytoplasmic droplets of fat resorption (arrow) and prominent nucleoli (arrow)

Glomerulus with glomerulomegaly from an extremely obese patient and glomerulus without glomerulomegaly from a control of the same age

Electron microscopy. Large-sized podocyte with intracytoplasmic lipids and focal foot process fusion (uranyl acetate and lead citrate stain, original magnification)

Mild fusion of podocytes and condensations of cytoskeletal filaments with a parallel orientation to the glomerular basement membrane

Serra A et al. Kidney Int; (2008) 73, 947–955

Obesity-associated focal segmental glomerulosclerosis (OB-FSGS)

- Proteinuria (frequently in nephrotic range)
- Lack of oedema, hypoalbuminemia, hypoproteinemia and lipds disorders
- Decrease GFR in 50% patients

- Histopathology
  - Glomerulomegaly
  - FSGS
- Treatment:
- loss on weight, ACEI / ARBs

Praga M. et al., Nephrol. Dial. Transplant., 2001, 16, 1790-1798

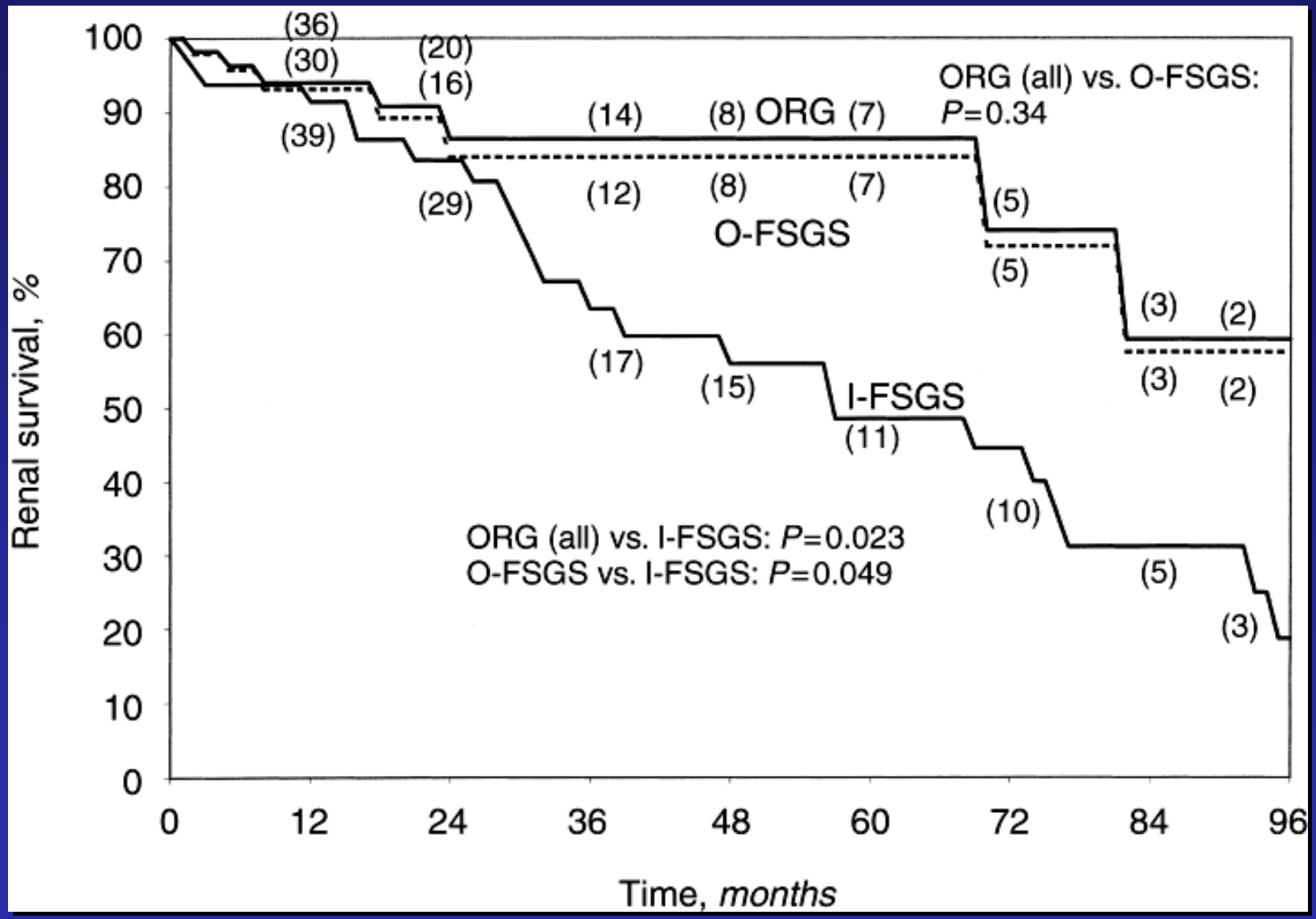
Praga M. et al., Nephrol. Dial. Transplant., 2002, 17, 1157-1159

Renal biopsy findings in OB-FSFS and I-FSGS

	Per cent of normal glomeruli	Per cent of glomeruli with FSG lesions	Per cent of glomeruli with GGS	Glomerular diameter (μm)
OB-FSG (*n*=15)	61±24	19±23	18±18	256±24
I-FSG (*n*=15)	57±20	24±12	18±20	199±26 *P*<0.001

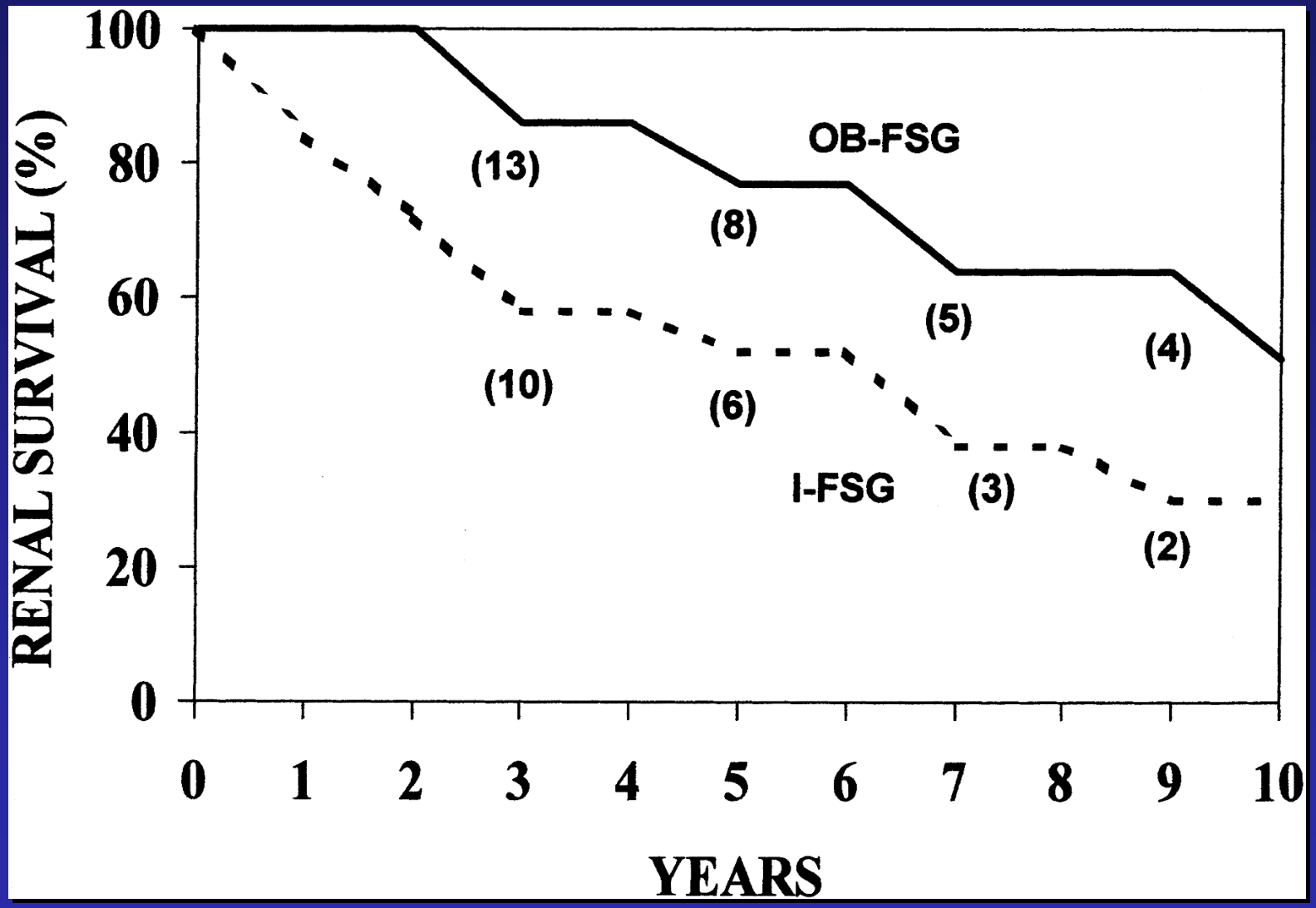
Praga M. et al.: Nephrol Dial Transplant. 2001, 16, 1790-1798

Renal survival (endpoints defined as doubling of serum creatinine or ESRD) over time in ORG, O-FSGS, and control I-FSGS



Kambham N. et al.: Kidney Int. 2001, 59: 1498-1509

Renal survival in patients with obesity-associated FSGS (OB.-FSGS) and idiopathic FSGS (I-FSGS)



Praga M. et al.: Nephrol. Dial. Transplant., 2001, 16, 1790-1798

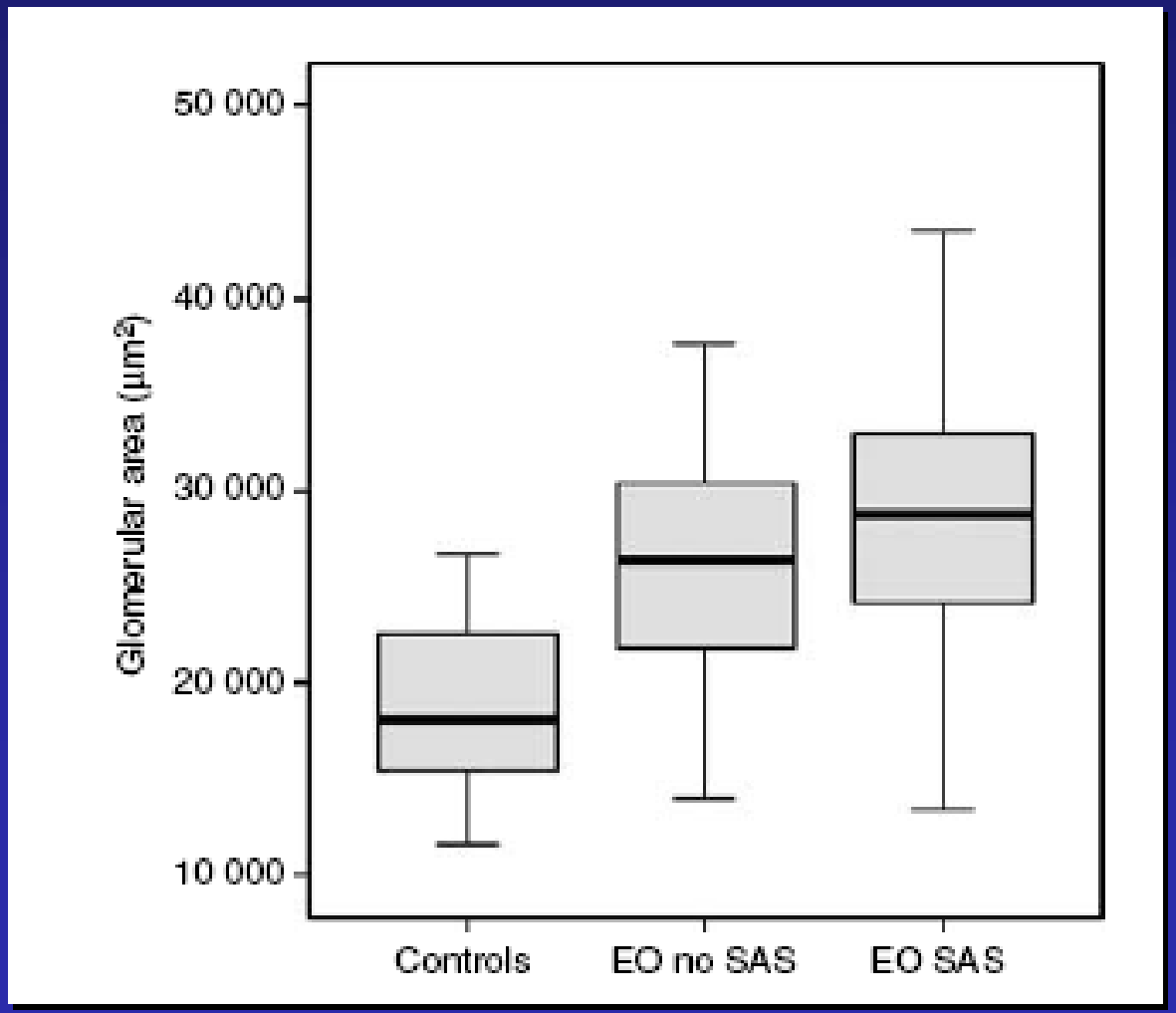
Risk factors associated with glomerular lesions

in extremely obese patients and normal-weight controls

	Univariate		Multivariate[b]	
	OR 95% CI	*P*-value	OR 95% CI	*P*-value
Gender (male)	1.79 (0.90–3.57)	0.097	—	—
Age (years)[c]	1.00 (0.73–1.37)	0.977	—	—
BMI (kg m^{-2})[d]	1.99 (1.59–2.50)	<0.001	1.99 (1.59–2.50)	<0.001
Systolic blood pressure (mm Hg)[c]	1.51 (1.15–1.98)	0.003	—	—
Diastolic blood pressure (mm Hg)[c]	1.43 (1.05–1.96)	0.026	—	—
Serum fasting glucose (mmol l^{-1})	1.29 (0.96–1.74)	0.087	—	—
Serum total cholesterol (mmol l^{-1})	1.21 (0.84–1.74)	0.302	—	—
Smoker	0.77 (0.35–1.68)	0.508	—	—

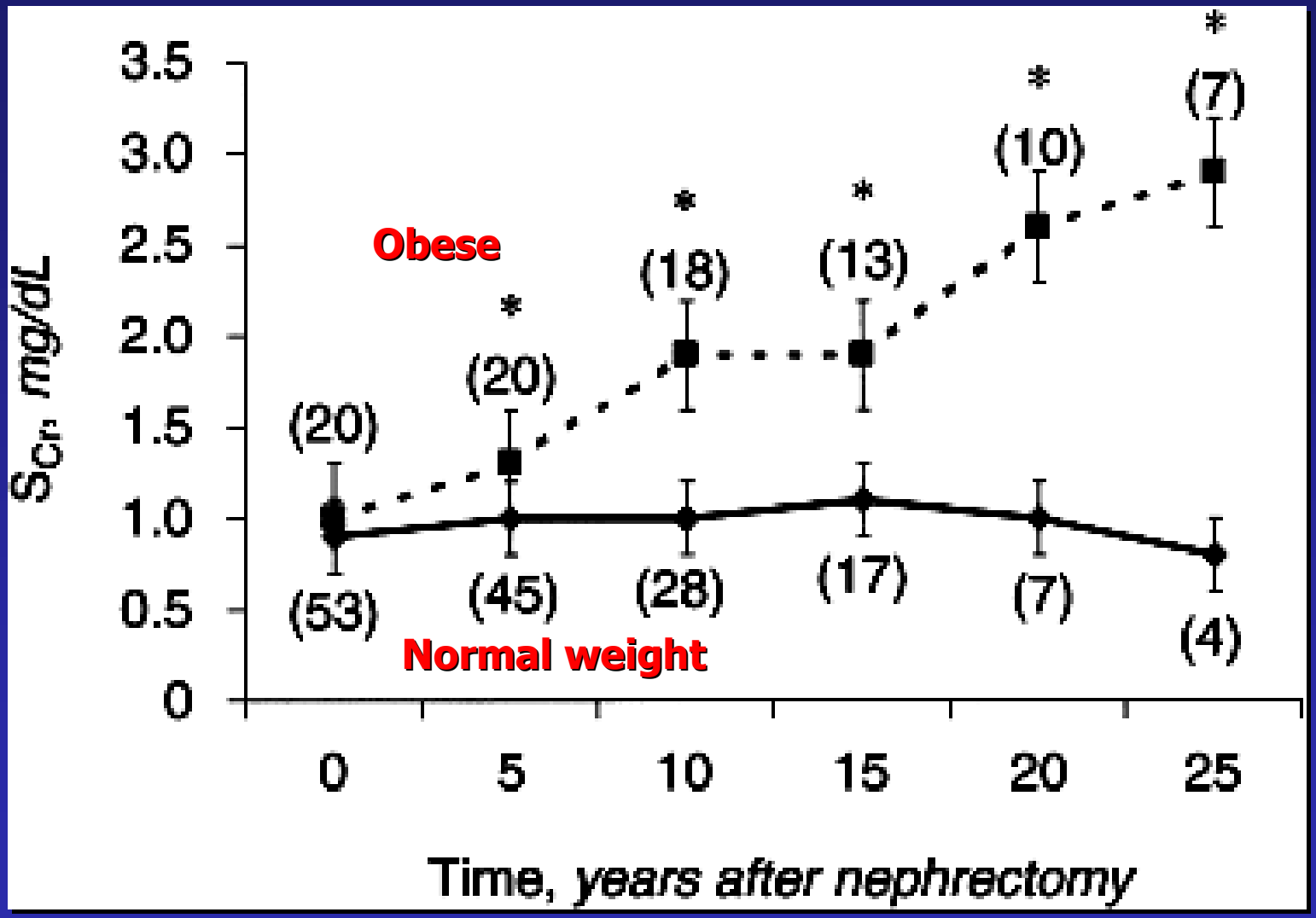
Serra A et al. Kidney Int; (2008) 73, 947–955

Glomerular areas in extremely obese (EO) patients with orwithout sleep apnea syndrome (SAS) and in controls



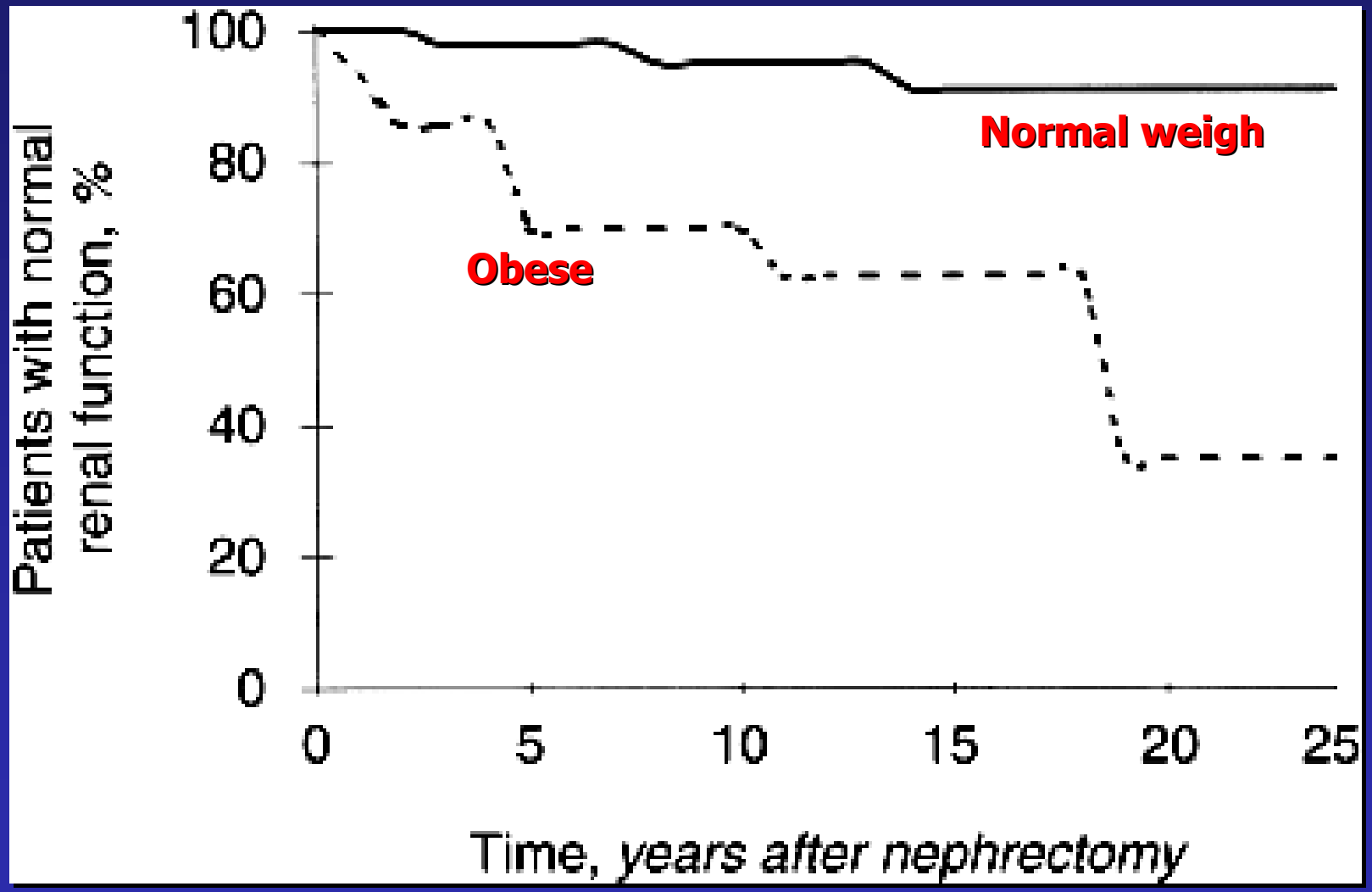
Serra A et al. Kidney Internat (2008) 73, 947–955

Evolution of serum creatinine in obese vs normal weight patients after unilateral nephrectomy



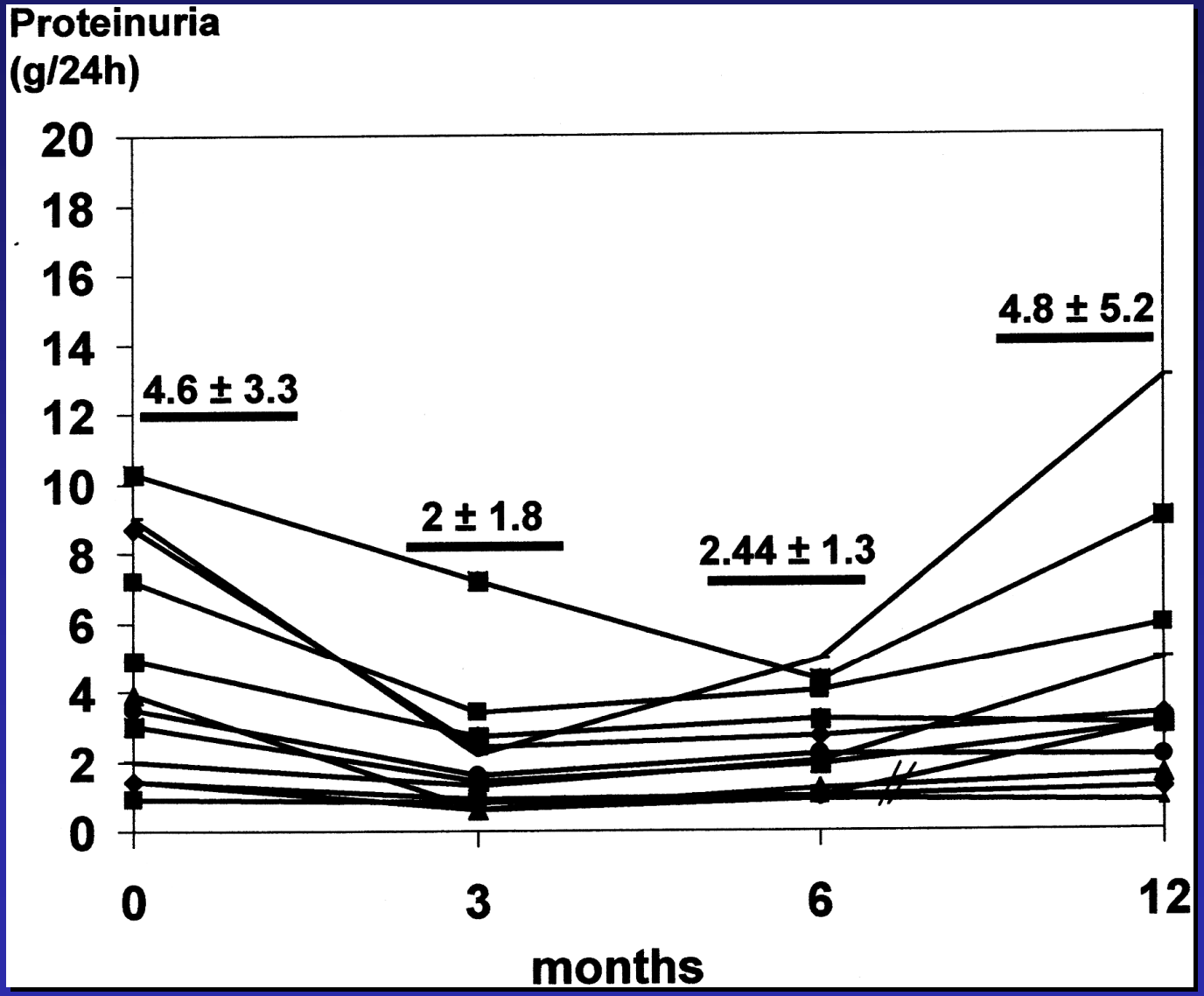
Praga M. et al. Kidney Int., 2000, 58: 2111-2118

Probability of normal renal function in obese (dashed line) andnonobese (solid line) patients (log-rank test, *P , 0.001)* after unilateral nephrectomy.



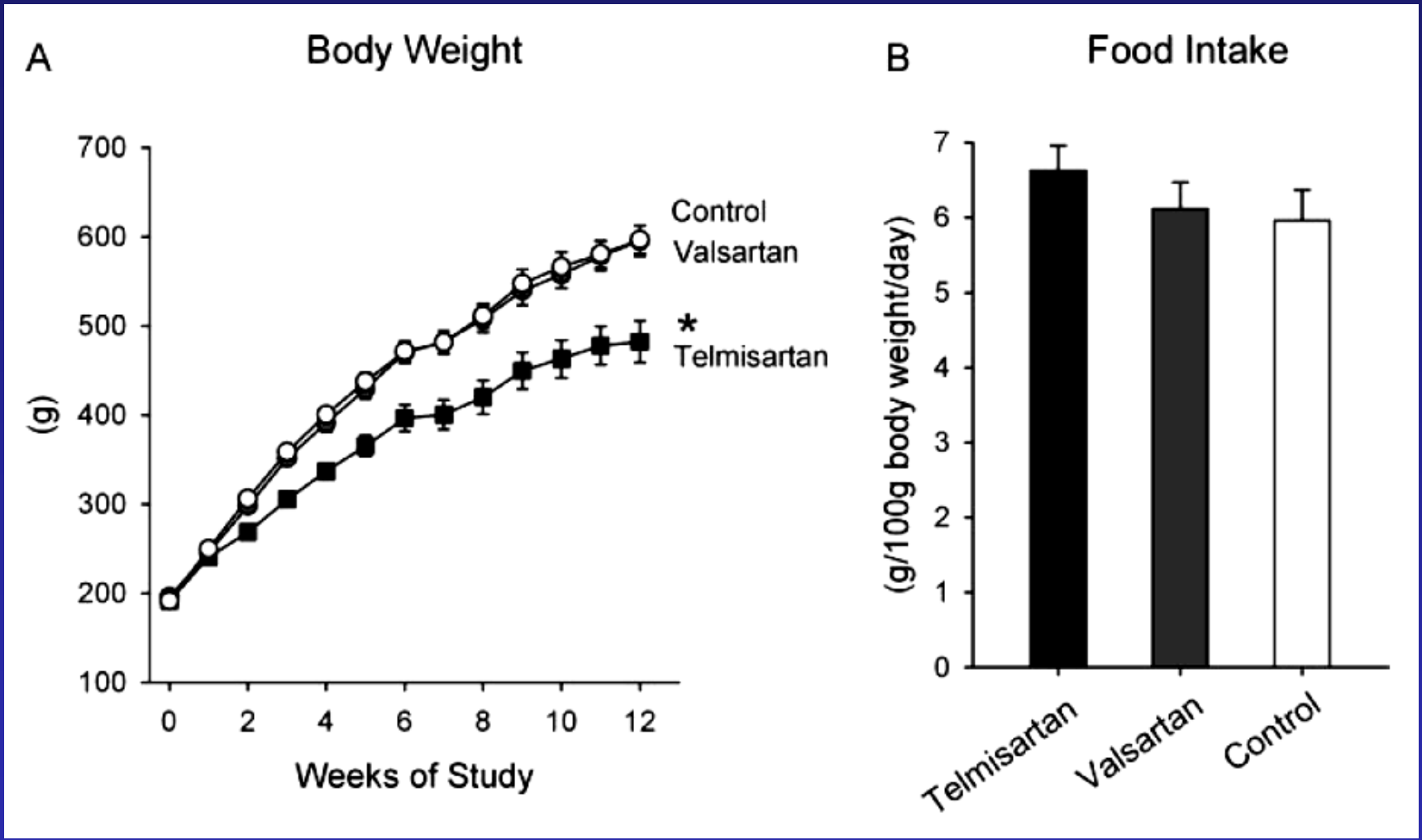
Praga M. et al., Kidney Int., 2000, 58: 2111-2118

Evolution of proteinuria after ACE-I treatment in obesity associated FSGS



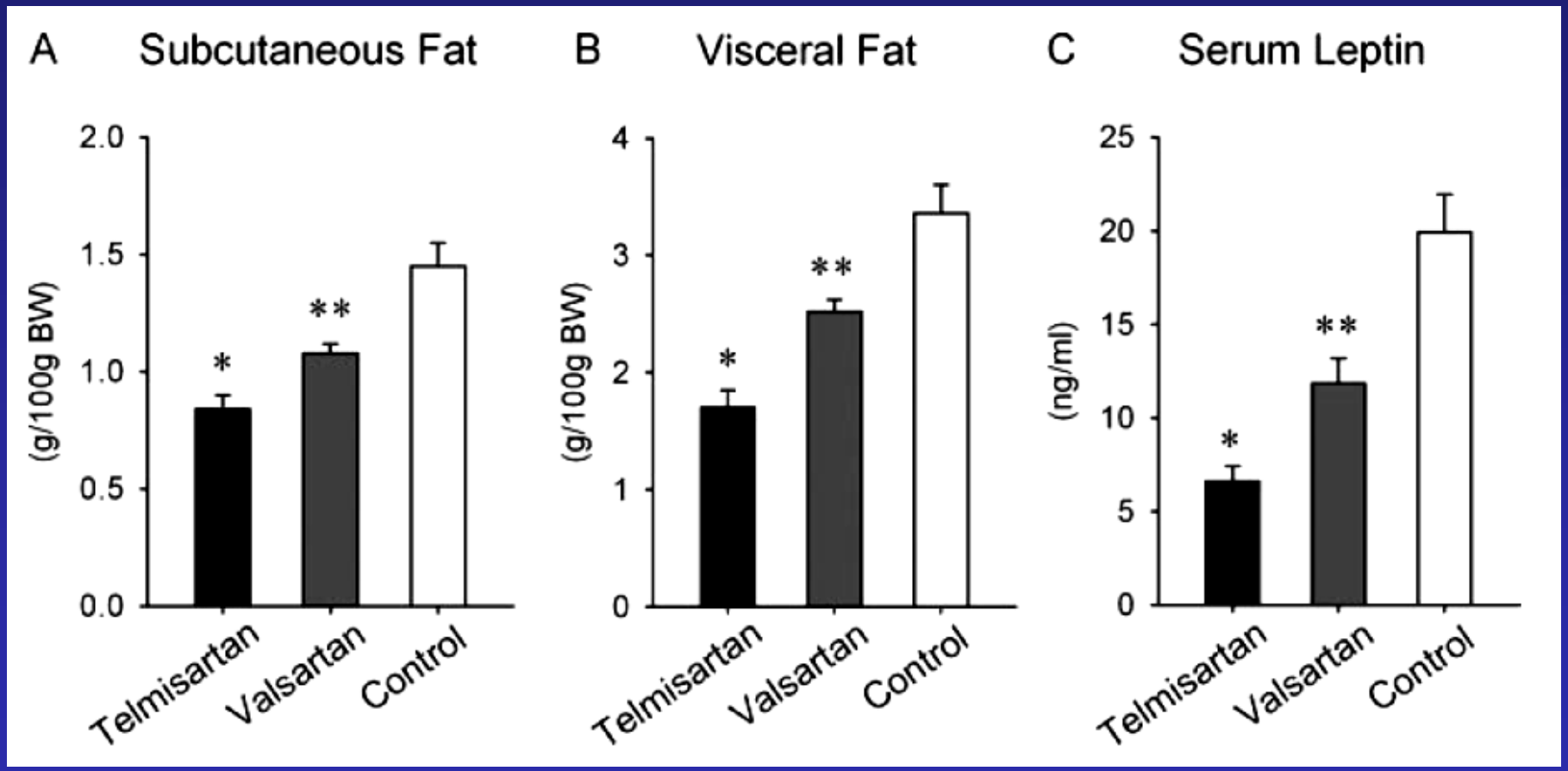
Praga M. et al., Nephrol. Dial. Transplant., 2001, 16: 1790-1798

Body weight and food intake in rats treated with telmisartan, valsartan, or in untreated controls

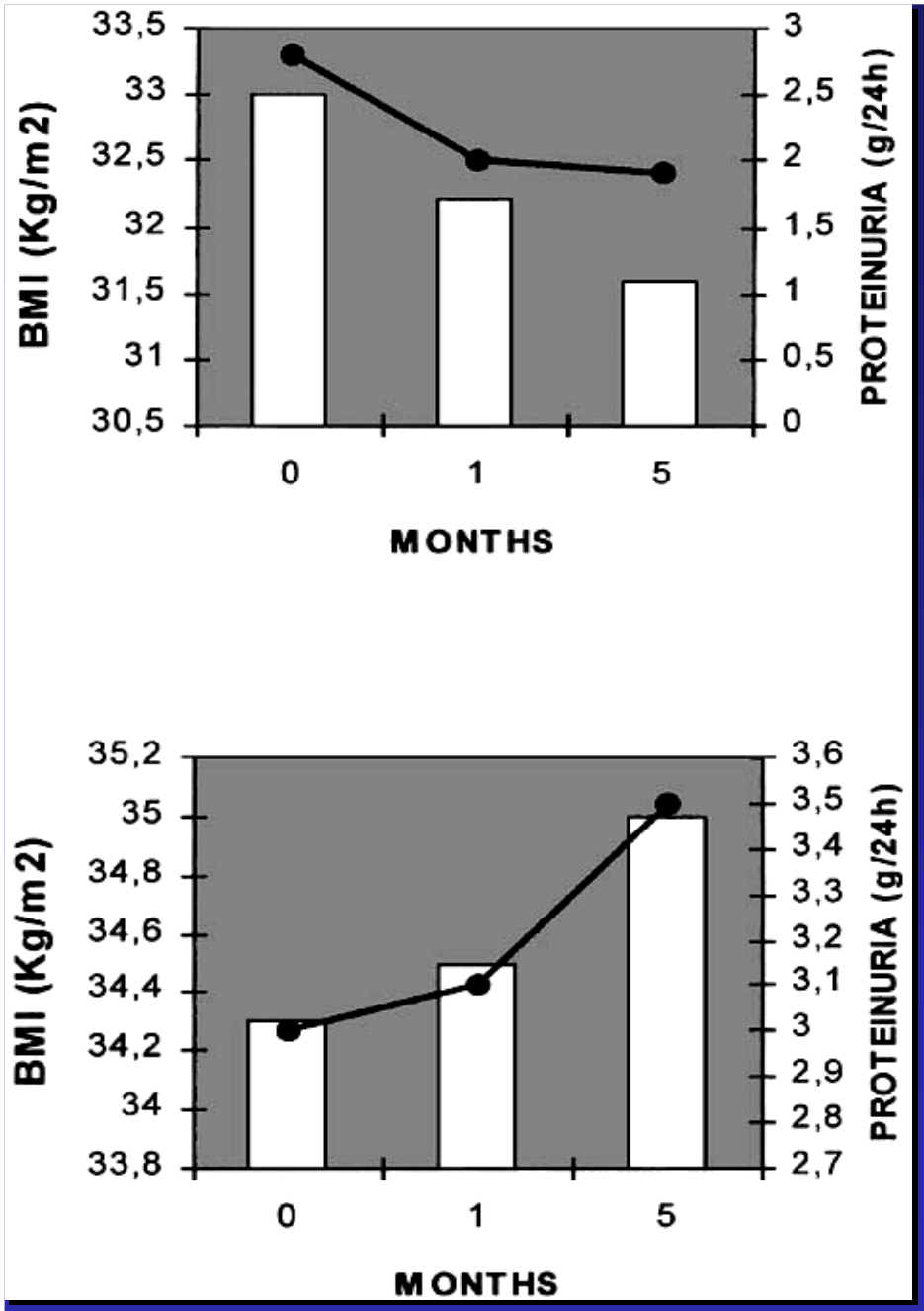


Sugimoto K., et al., Hypertension, 2006, 47, 1003-1009

Fat mass and serum leptin levels in rats treated with telmisartan, valsartan or in untreated controls



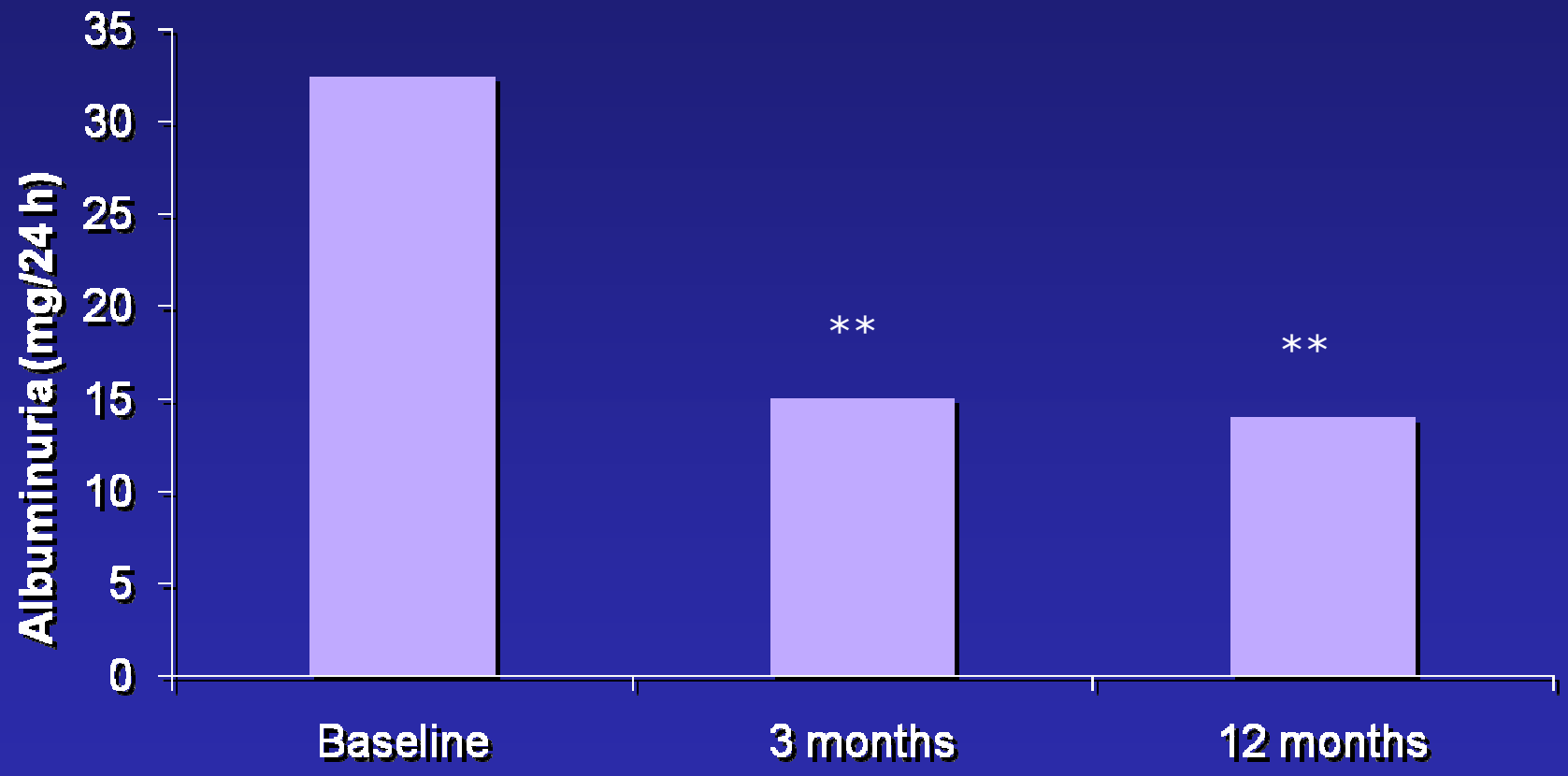
Sugimoto K. et al., Hypertension, 2006, 47, 1003-1009



Changes in BMI (▬) and proteinuria (line) in the (top) diet group and (bottom) control group.

Morales E. et al., Am. J. Kidney Dis., 2003, 41: 319-327

Telmisartan decrease albuminuria in obese patients with hypertension

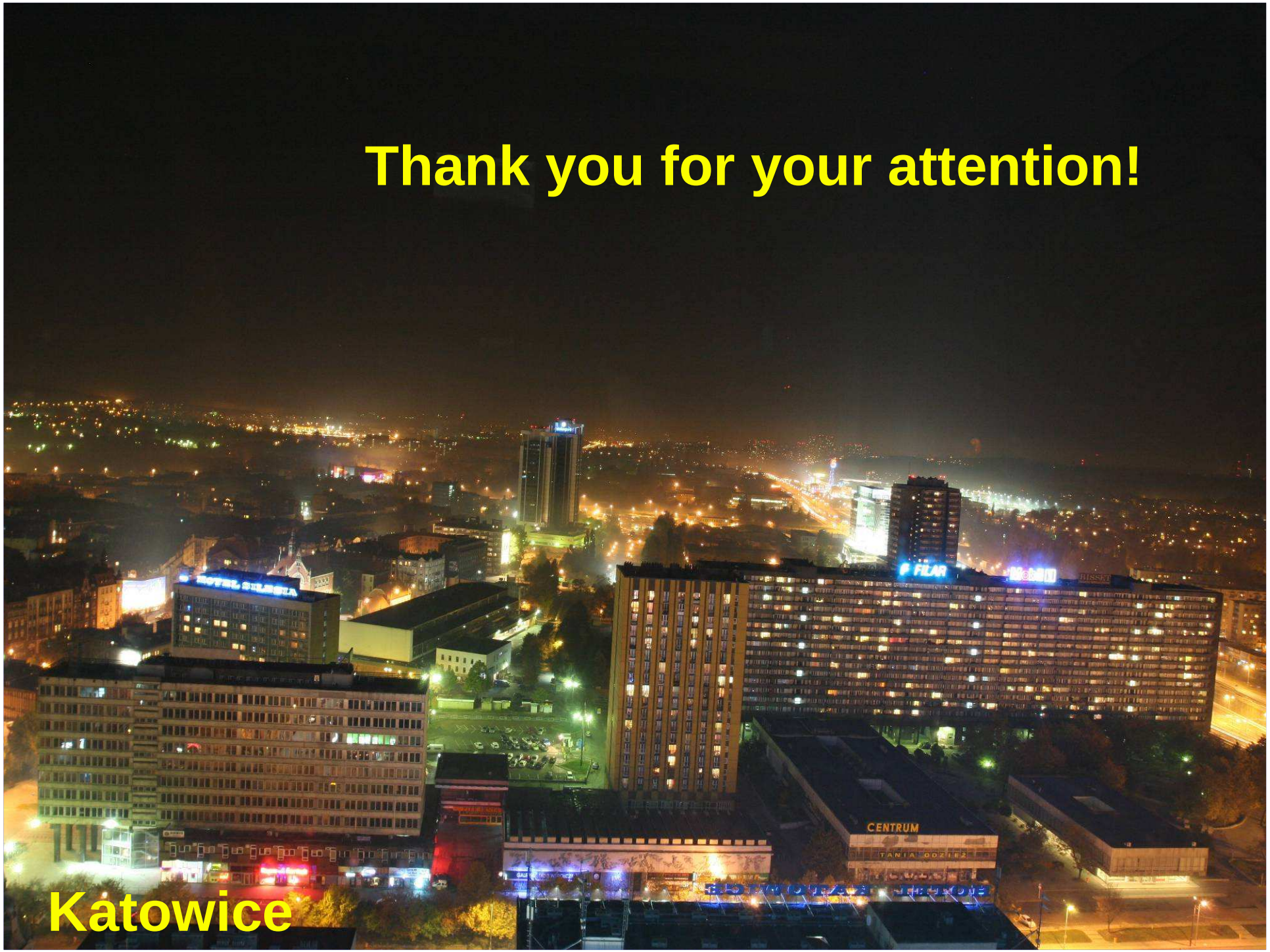


** P<0,01 vs baseline

Redón i wsp. *Pharmacogenomics J.* 2005;5:14–20

Summarize

- Obesity is important factor associated with:
  - obesity-associated focal segmental glomerulosclerosis (FSGS)
  - progression of others already existing (np. IgA nephropathy, ADPKD)
  - progression of kidney graft nephropathy
  - Increase probability of preeclampsia


Thank you for your attention!
Katowice
HOTEL SILESIA
FILAR
CENTRUM

Conclusion:

Obesity has been shown to increase the risk of both the development and the progression of renal failure, even after correction for other comorbid conditions

- **Szczury z nadciśnieniem samoistnym i otyłe szczury Zucker wykazują oporność na efekt natriuretyczny leptyny**

  Villarved D. et al., Am. J. Physiol., 1998, 275, R2056-R2060

- **To osłabienie działania natriuretycznego i diuretycznego leptyny może być spowodowane przez wzrost podstawowej aktywności układu współczulnego u tych szczurów lub stymulacją układu współczulnego przez leptynę, co prowadzi do nasilenia reabsorpcji sodu**

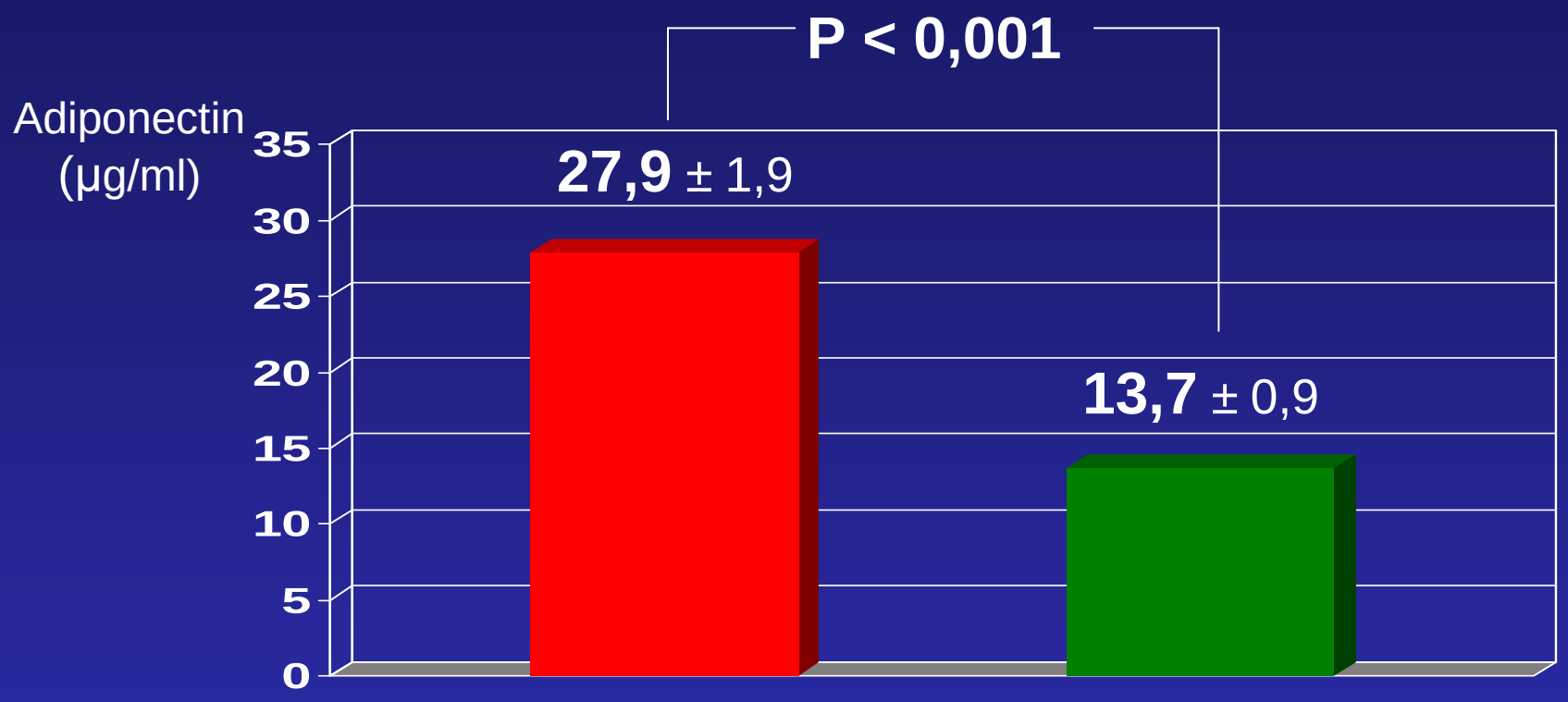
  Trayhum P. et al., Int. J. Obstrt. Relat. Metab. Disord. 1999, 23, 225-285

1. U osób otyłych oporność na uszkadzające kłębuszki działanie leptyny

2. Glomerulopatia towarzysząca otyłości wykazuje znamienną zależność od hiperfiltracji indukowanej zwiększonym poborem pokarmów oraz hipertriglicerydemii

Maddox D.A. i wsp., Kidney Int, 2002, 62, 208-219

Stężenie adiponektyny u hemodializowanych chorych (HD)



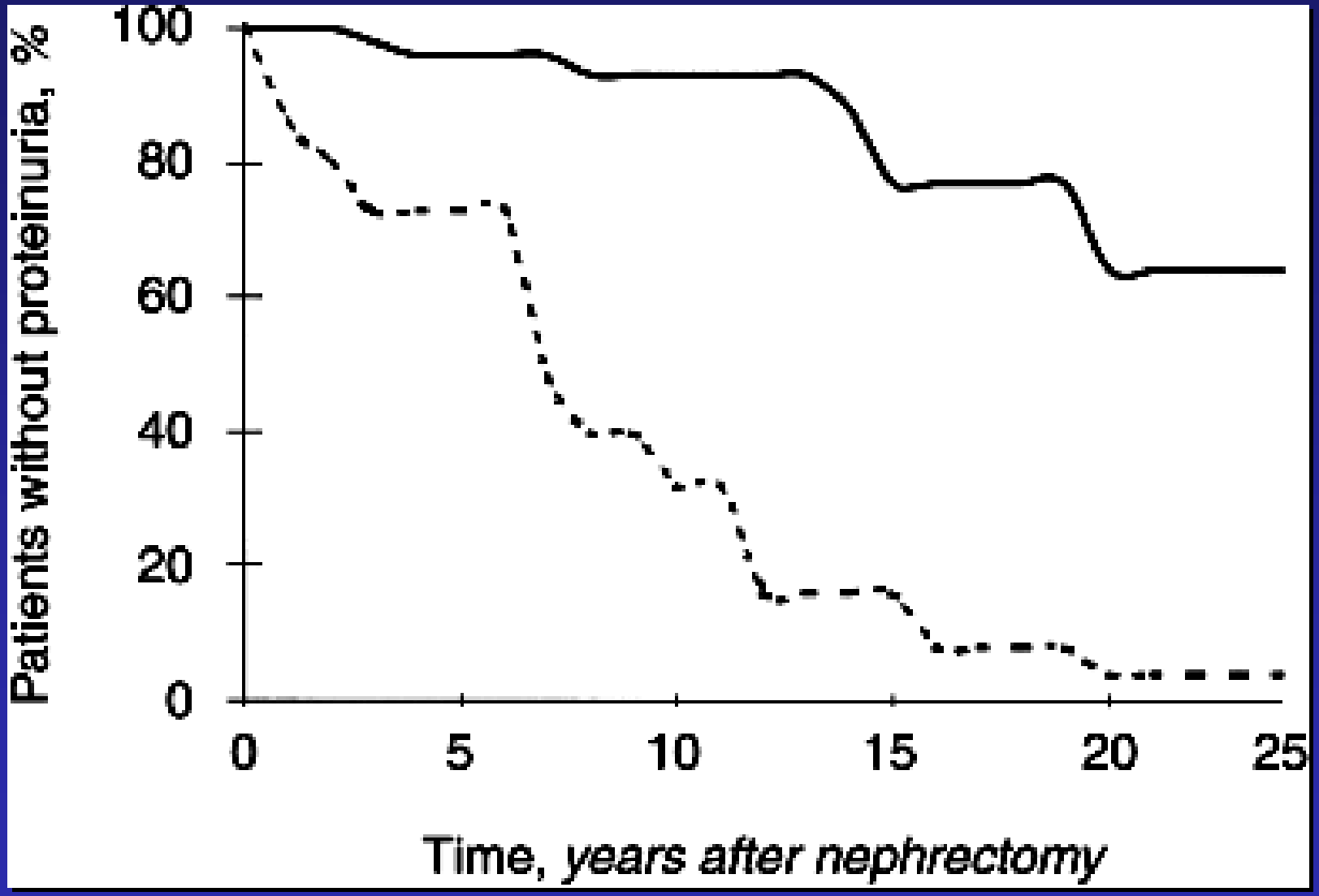
	HD	Healthy subjects
n	71	33
Age (years)	47 ± 2	50 ± 2

A. Więcek et al., Am J Soc Nephrol, 2002, 13, 498A

- Hamowanie układu RAS może zwiększać liczbę młodych, świeżo zróżnicowanych adipocytów które są bardziej insulinowrażliwe niż starsze, większe adipocyty

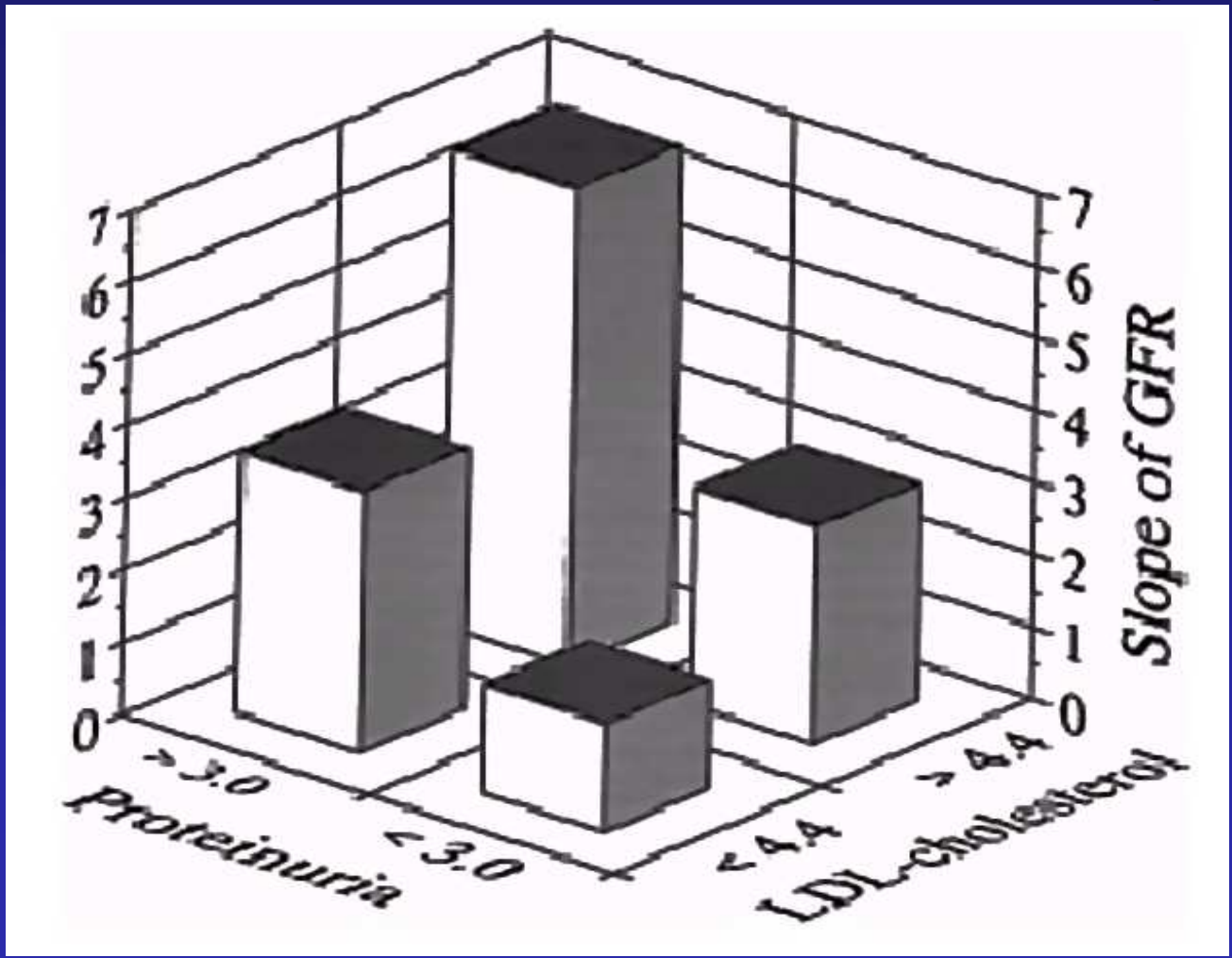
- Fakt ten może wyjaśniać obserwacje, że hamowanie układu RAS może zmniejszać ryzyko rozwoju cukrzycy typu 2

Probability of negative proteinuria in obese (dashed line) and nonobese (solid line) patients

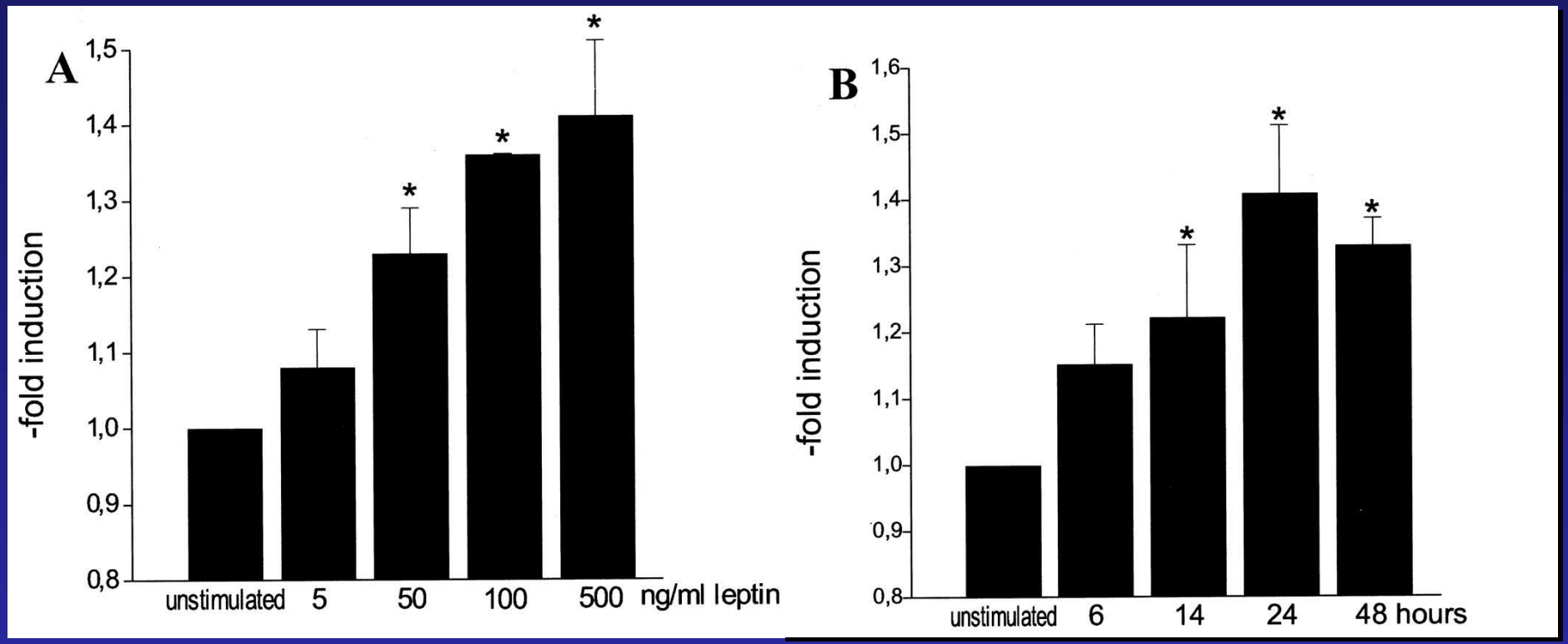


Praga M. et al. Kidney Int 2000, 58: 2111-2118

Rate of progression of renal insuciency (slope of GFR expressed as the change in ml/min per year) in relation to high and low levels of LDL cholesterol, in mmol/l, and the amount of urinary total protein excretion, above and below a cut-o level of 3.0 g per 24 h.



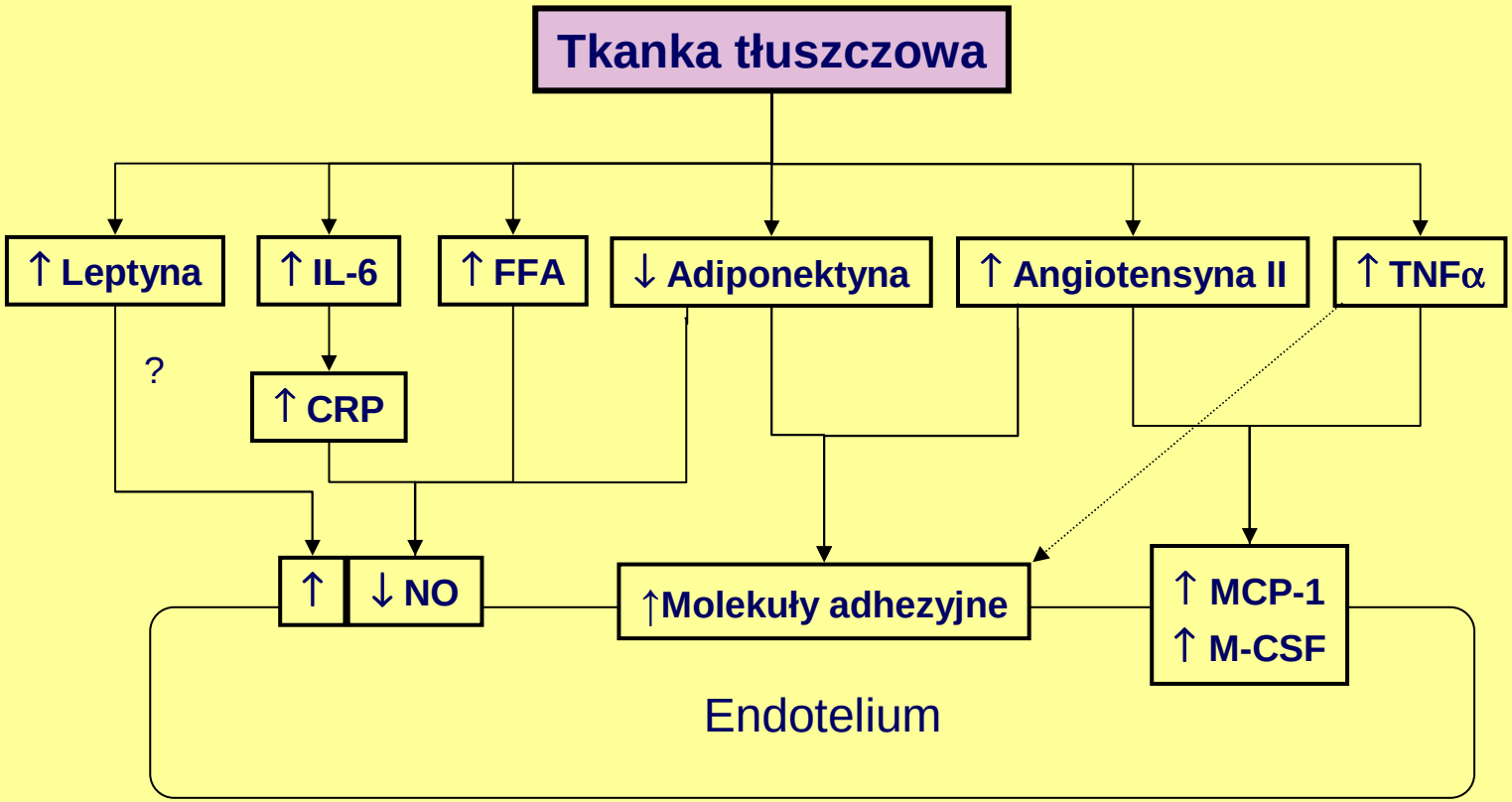
Samuelsson O i wsp., Nephrol Dial Transplant, 1997; 12; 1908-1915



Endothelin-1 expression in HUVECs is induced by leptin. HUVECs were incubated with various concentrations of leptin for 24 hours (A) and with 500ng/mL leptin for several time periods (B) to demonstrate dose- and time-dependent ET-1 induction. ET-1 content in cell culture supernatants was measured with ELISA. The results represent the mean±SEM of at least 3 experiments. *$P<0.05$ compared with unstimulated HUVECs.

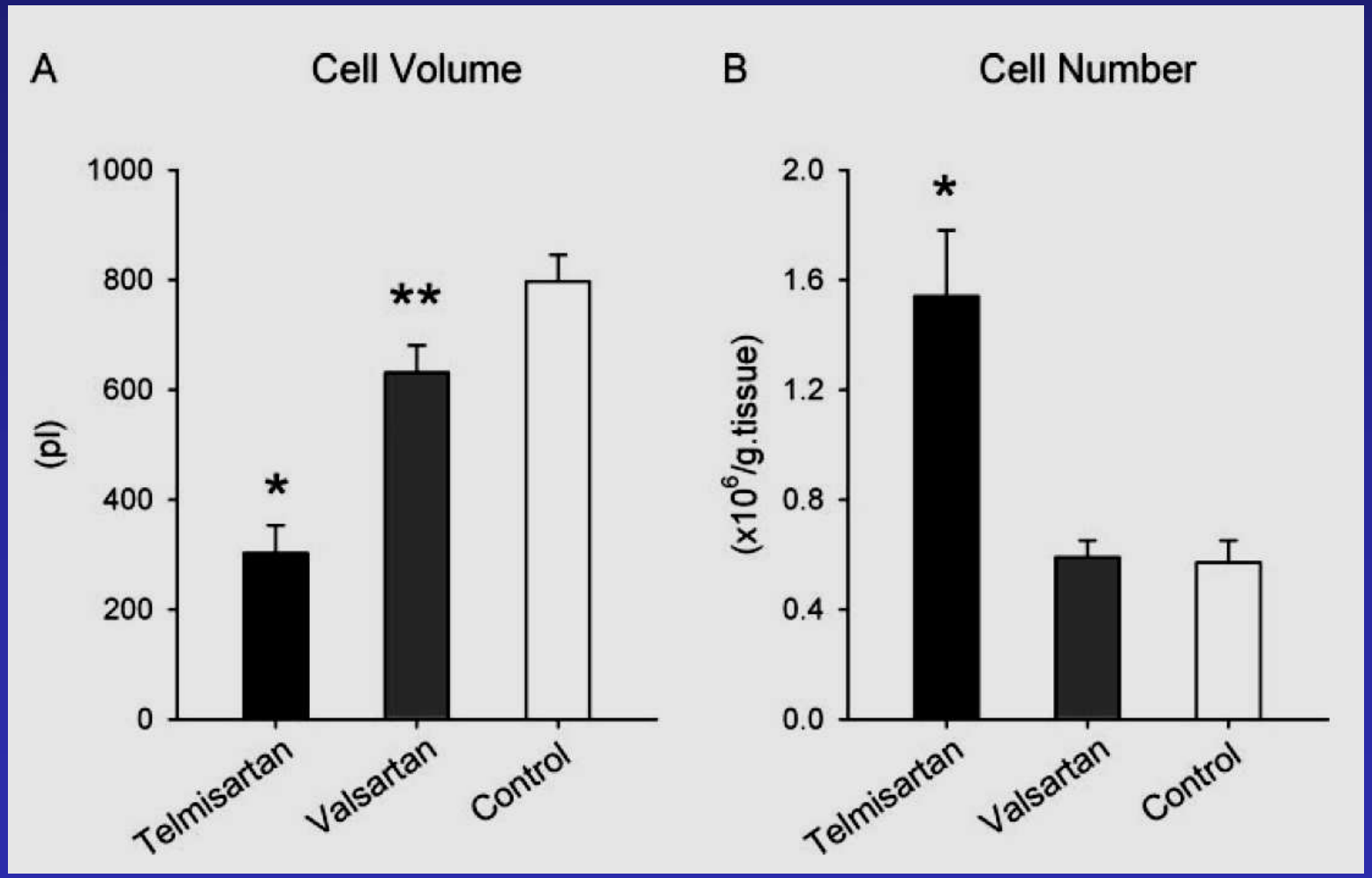
Quehenberger P et al.: Circ Res. 2002, 90: 711-718

Wpływ czynników wytwarzanych przez tkankę tłuszczową na śródbłonek naczyń



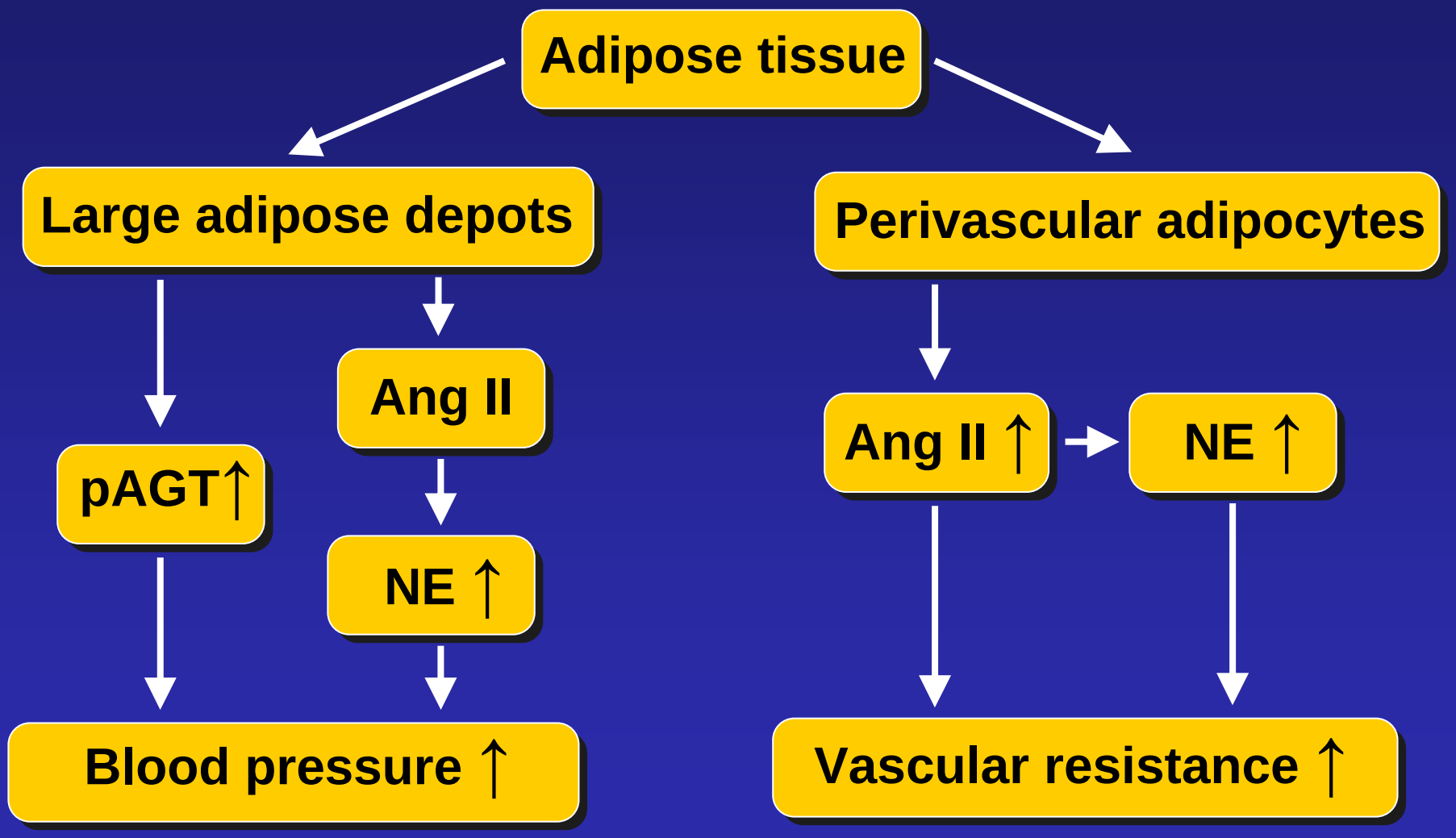
Chudek J., Więcek A., Pharmacol. Rev., 2006

Wpływ leczenia telmisartanem lub walsartanem vs grupa kontrolna na objętość i liczbę adipocytów u szczurów



Sugimoto K et al. Hypertension 2006, 47, 1003-1009

Regulacja czynności układu sercowo-naczyniowego przez AGT i Ang II uwalniane z tkanki tłuszczowej



Engeli S. et al., Horm. Metab. Res., 2000, 32, 490

Tkanka tłuszczowa uczestniczy w:

- Regulacji łaknienia
- Regulacji ciśnienia tętniczego
- Insulinooporności
- Angiogenezie
- Powikłaniach miażdżycowych
- Zaburzeniach hemostazy i hematologicznych
- Regulacji układu odpornościowego
- Regulacji funkcji neuroendokrynnych
- Glomerulopatii zależnej od otyłości

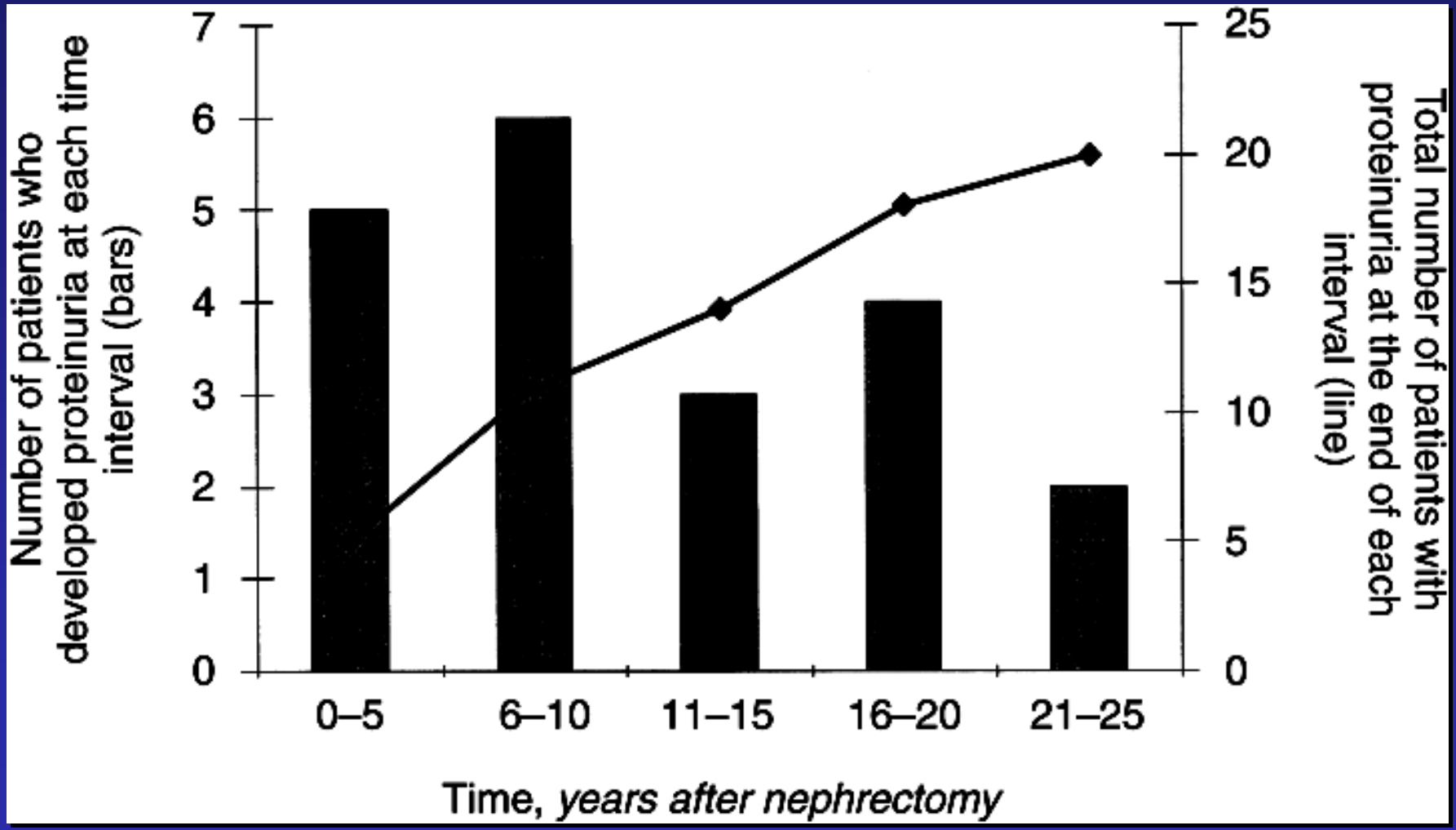
Dlatego też przemiany zachodzące w tkance tłuszczowej powinny interesować również nefrologa !

Rola leptyny w patogenezie przewlekłej choroby nerek (CKD)

- Leptyna stymuluje proliferację komórek śródbłonka kłębuszków nerekowych zarówno in vitro jak i in vivo oraz transkrypcję i sekrecję TGRβ1 – cytokiny uczestniczącej w procesie włóknienia
- Podawanie leptyny u szczurów powoduje białkomocz oraz rozplem komórek macierzy kłębuszków nerkowych

Wolf G. et al., Kindey Int., 1999, 56, 860-872

Liczba chorych u których występuje białkomocz w kolejnych latach po jednostronnej nefrektomii u osób otyłych



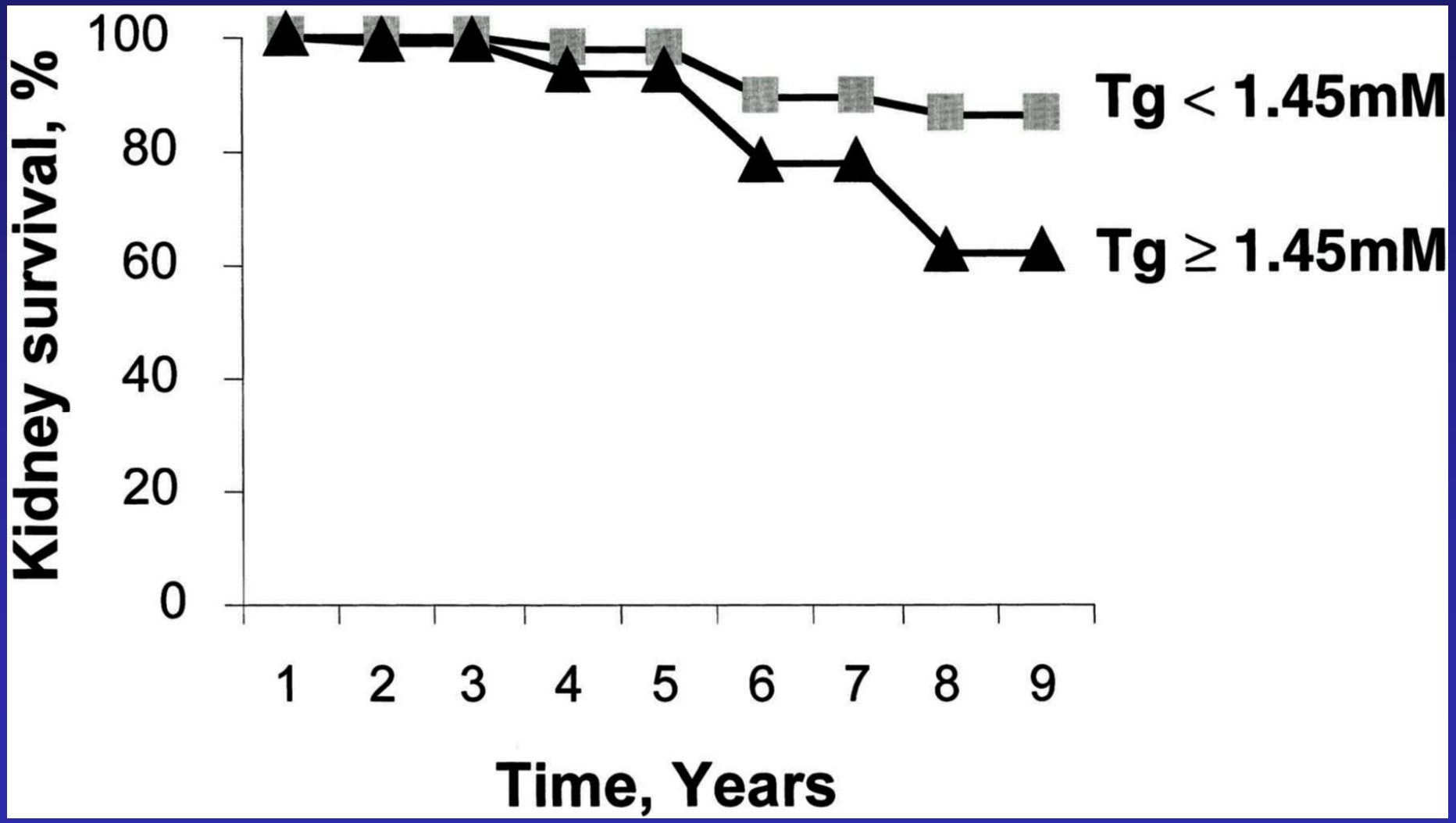
Praga M. et al. Kidney Int., 2000, 58: 2111-2118

Podsumowanie

- W leczeniu uszkodzenia nerek w przebiegu otyłości korzystny wpływ wywiera:
  - Zmniejszenie (normalizacja) masy ciała
  - Inhibitory konwertazy (prylaty, ACEi)
  - Blokery receptora AT_1 dla AII (sartany, ARBs); szczególnie korzystne działanie telmisartanu
  - Blokery receptora mineralokortykoidowego (badania doświadczalne z eplerenonem)

Obesity- the public health problem in Western Countries

Adjusted survival-curve obtained from a Cox proportional hazard analysis for two levels of baseline triglycerides (Tg) in patients with PCKD and GN



Massy ZA i wsp., Nephrol Dial Transplant, 1999; 14; 2392-2397

The most important adipokines, chemokines release by adipocytes and matrix of adipose tissue responsible for CV and renal disease (1)

- PA I-1
- TGF-β
- Tissue factor (TF)
- Complement factors (e.g. adipsin)
- Adipocyte complement- related protein (Adipo-a)
- TNF-α
- Acylation stymulation protein (ASP)
- Agouti Protein
- Angiotensinogen, Renin, ACE
- Chymase, cathepsin D,G
- Angiotensin II
- Prostaglandins (PGI_2, $PGF_{2\alpha}$)
- Insulin growth factor-1 (IGF1)

Pooled RR and 95% CI of KD in 18 general population cohort studies according to BMI categories

	Number of cohorts	BMI categories			
		Underweight (BMI < 18.5)	Normal (18.5 ≤ BMI < 25)	Overweight (25 ≤ BMI < 30)	Obesity (BMI ≥ 30)
All studies	18	0.92 (0.74–1.15)	1 (ref)	1.40 (1.30–1.50)	1.83 (1.57–2.13)
Gender difference					
All studies					
Men	11	0.63 (0.48–0.85)	1 (ref)	1.31 (1.18–1.45)	1.49 (1.36–1.63)[b]***
Women	11	1.11 (0.98–1.25)	1 (ref)	1.41 (1.32–1.50)	1.92 (1.78–2.07)
KD excluding kidney cancer/RCC					
Men	3	0.73 (0.52–1.03)	1 (ref)	1.59 (1.12–2.26)	1.33 (1.08–1.63)[b]**
Women	4	1.14 (1.00–1.30)	1 (ref)	1.48 (1.32–1.66)	1.99 (1.77–2.24)
Kidney cancer/RCC					
Men	8	0.45 (0.27–0.77)	1 (ref)	1.21 (1.15–1.27)[b]**	1.53 (1.38–1.69)[b]**
Women	7	0.86 (0.59–1.26)	1 (ref)	1.38 (1.28–1.49)	1.87 (1.69–2.07)
BMI assessment					
Directly measured	9	0.76 (0.56–1.04)	1 (ref)	1.38 (1.22–1.56)	1.78 (1.33–2.40)
Self-reported	9	1.07 (0.94–1.20)	1 (ref)	1.39 (1.27–1.53)	1.84 (1.56–2.17)
Specific KD outcomes					
KD excluding kidney			1 (ref)		
Cancer/RCC	8	1.08 (0.96–1.22)		1.42 (1.27–1.60)	1.95 (1.45–2.64)
CKD	3	1.30 (0.52–3.24)	1 (ref)	1.26 (1.10–1.45)	1.34 (0.86–2.09)
ESRD	2	NR[c]	1 (ref)	1.68 (1.49–1.90)	4.07 (2.87–5.76)
Kidney stone	3	1.08 (0.95–1.22)	1 (ref)	1.41 (1.18–1.69)	1.75 (1.36–2.25)
Kidney cancer/RCC	10	0.70 (0.51–0.95)	1 (ref)	1.31 (1.23–1.40)	1.71 (1.53–1.93)

BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; ESRD, end-stage renal disease; KD, kidney disease; RR, relative risk; RCC, renal cell carcinoma.
[a]Data from one study[5] shown in Table 1 are excluded in this table.
[b]Gender difference, **$P < 0.01$; ***$P < 0.001$.
[c]NR, No results were reported for underweight.

Wang Y. et al., Kidney Int., 2008; 73 18-23

- In this retrospective cohort study of 320 252 adults who were followed for 15 to 35 years, the rate of ESRD increased in stepwise manner as body mass index (BMI) increased.

- Age-, sex-, and race-adjusted rates of ESRD increased from 10 per 100 000 person-years among those with normal weight (BMI, 18.5 to 24.9 kg/m2) to 108 per 100 000 among those with extreme obesity (BMI 40 kg/m2).

- This relationship was not affected by blood pressure levels or diabetes

Implications

High BMI is a potentially modifiable risk factor for ESRD.

Hsu Ch. Ann. Internal Med., 2006; 144: 21-28

The most important adipokines, chemokines release by adipocytes and matrix of adipose tissue responsible for CV and renal disease (2)

- Vascular endothelial growth factor (VEGF)
- Macrophage inhibitor factor (MIF)
- Sex hormones (in women: testosterone, estradiol and estrone)
- Glucocorticoids
- Leptin
- Adiponectin
- Resistin
- Visfatin
- IL-6
- NO
- PPAR-γ
- Atrial natriuretic peptide (ANP)