Obesity and Dysmetabolism as Risk Factors for Chronic Kidney Disease

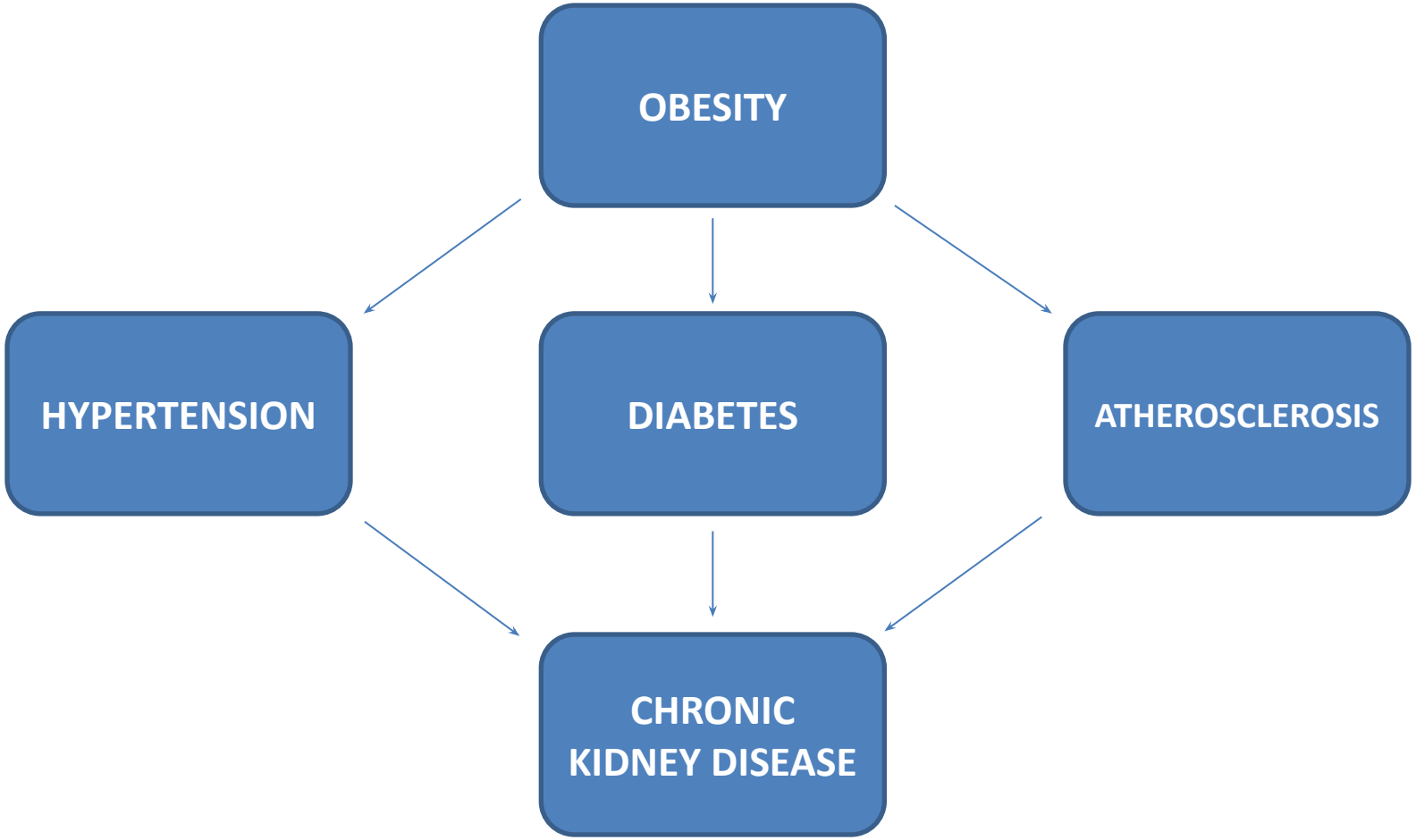
Matthew R. Weir, MD
Professor and Chief
Division of Nephrology
University of Maryland School of Medicine
mweir@som.umaryland.edu

Disclosure

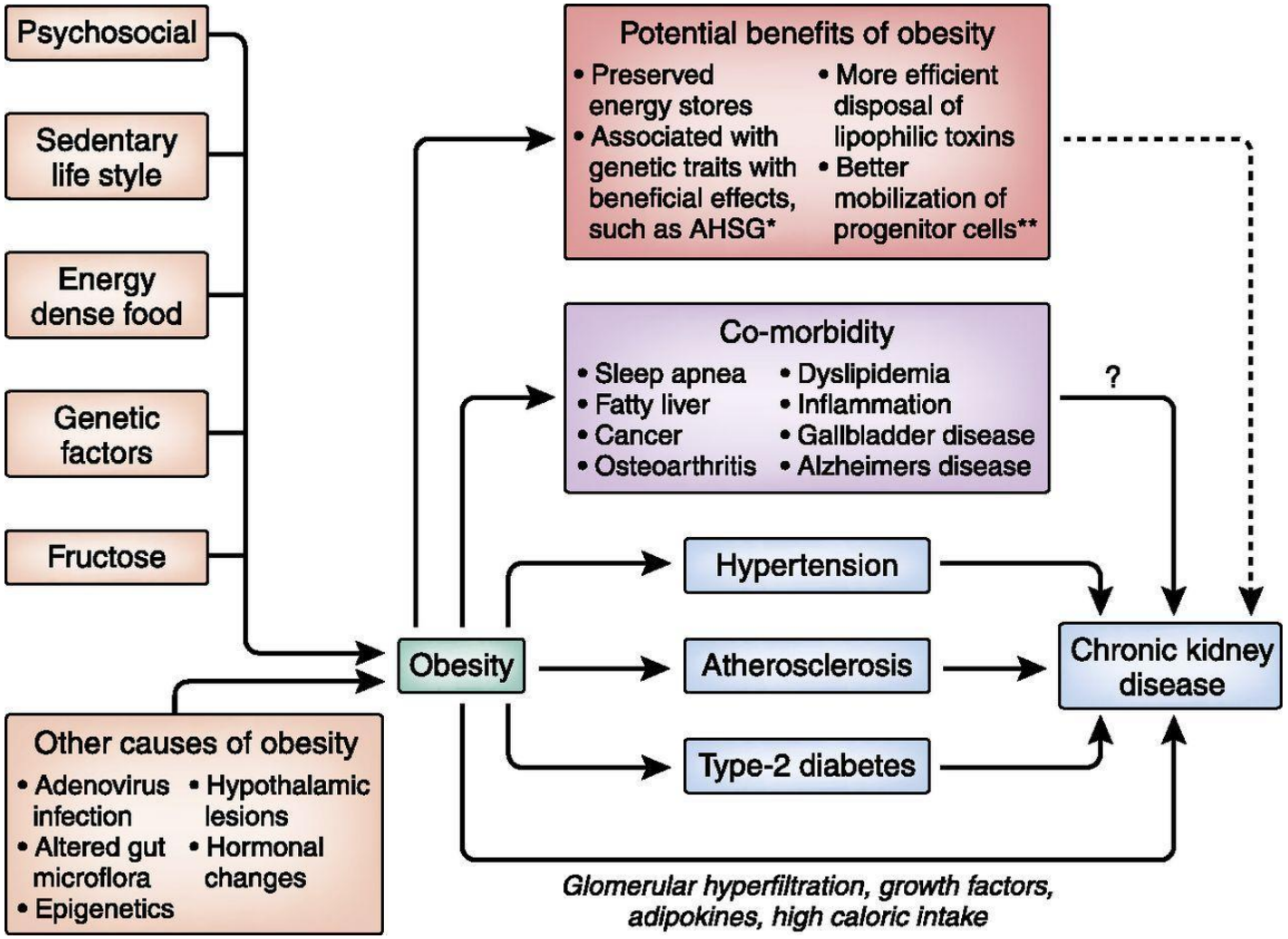
Scientific Advisor: Johnson and Johnson, AstraZeneca, Merck, Bayer, Vifor, Boehringer-Ingelheim, NovoNordisk, Akebia

Grant Funding: NIDDK: R01 DK120886, U01 DK116095, R01 DK 132271, U01 DK106102, U01 DK129884

Obesity and Chronic Kidney Disease are Major Public Health Problems!


OBESITY
HYPERTENSION
DIABETES
ATHEROSCLEROSIS
CHRONIC
KIDNEY DISEASE

Relationships between obesity and chronic kidney disease



Peter Stenvinkel et al. JASN 2013;24:1727-1736

Epidemiology

- Patients without DM or HTN had a 3-fold increase in risk of CKD if overweight at age 20
- Higher baseline BMI remained an independent risk factor for ESRD even after adjustment for blood pressure and DM
- Obesity associated with a 70% increase risk of MAU
- Components of metabolic syndrome and CKD are strongly and consistently linked

Clinical Manifestations of Obesity-related CKD

- Obesity is an independent risk factor for CKD
- Metabolically unhealthy obesity/ metabolic syndrome as a risk factor for CKD
- Metabolically healthy obesity as a risk factor for CKD
- Obesity, itself, as a cause for HTN and DM
- Obesity enhances progression of pre-existing CKD
- Obesity promotes nephrolithiasis
- Obesity increases kidney donor risk for ESRD
- Obesity increases kidney transplant risk for DGF

Association of Body Mass Index with ESRD (Kaiser Permanente) (n=320,252 Adults)	
BMI (Kg/M^2)	**ODDS Ratio For ESRD (CI)**
18.5 – 24.9	1.0
25.0 – 29.9	1.87 (1.64 – 2.14)
30.0 – 34.9	3.57 (3.05 – 4.18)
35.0 – 39.9	6.12 (4.97 – 7.54)
>40.0	7.07 (5.37 – 9.31)

Hsu C, et al. Ann Intern Med 2006;144:21-28.

Definition of metabolic syndrome by WHO, NCEP ATP III, and IDF

WHO Definition	NCEP ATP III Definition	IDF Definition
Insulin resistance identified by type 2 diabetes or impaired fasting glucose or impaired glucose tolerance or insulin resistance (by insulin clamp) plus two or more of the following: •BMI >30 kg/m^2 and/or waist:hip ratio >0.9 (male) and >0.85 (female) •Triglycerides ≥150 mg/dl •BP ≥140/90 mmHg and/or antihypertensive drugs •HDL cholesterol <35 (male) and <39 (female) •Microalbuminuria (albumin excretion rate ≥20 µg/min) or albumin:creatinine ratio ≥30 mg/g	Metabolic syndrome is defined by three or more of the following risk factors: •Waist circumference >88 cm (women) and >102 cm (men) •Triglycerides ≥150 mg/dl •HDL cholesterol <40 (male) and <50 (female) •BP ≥130/85 mmHg •Fasting glucose level ≥110 mg/dl	Central obesity (waist circumference, ethnicity specific) plus two or more of the following: •Triglycerides ≥150 mg/dl or treatment for this abnormality •HDL cholesterol <40 (male) and <50 (female) or specific treatment •BP ≥130/85 mg/dl or pharmacologic treatment

Cirillo, et al. JASN December 2006 vol. 17 no. 12 suppl 3 S165-S168

Association of Metabolic Syndrome and CKD in U.S. Adults (n=6217, NHANES 3)	
Metabolic Syndrome Components	**ODDS Ratio For CKD (CI)**
0, 1	1.0
2	2.21 (1.16 – 4.24)
3	3.38 (1.48 – 7.69)
4	4.23 (2.06 – 8.63)
5	5.85 (3.11 – 11.0)

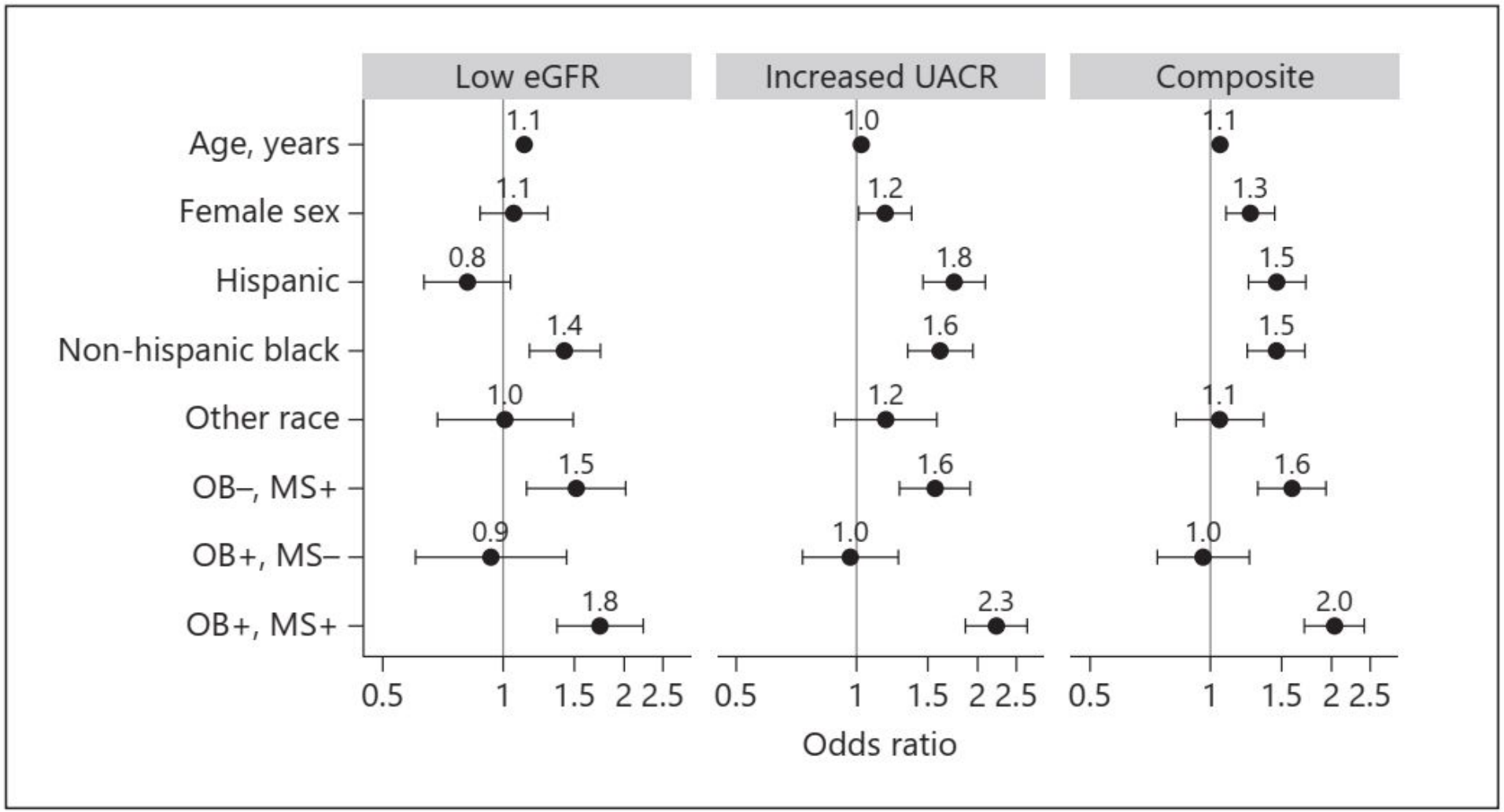
Chen, J, et. al. Ann Intern Med 2004; 140:167-174.

Metabolic Syndrome, Not Obesity is Associated with CKD

- n=12, 335 from NHANES 2005-2016
- Cross-sectional data
- Obese subjects without metabolic syndrome were younger and more commonly female

Ciardullo, et al. Am J Neph 2021;52:666-672

Multivariable logistic regression model assessing the contribution of OB and MS on the odds of reduced eGFR, increased UACR, and their combination.



Ciardullo, et al. Am J Neph 2021;52:666-672

Metabolically Healthy Obesity: Development of Chronic Kidney Disease

- Prospective cohort study
- Seoul, South Korea
- n= 62,249, mean age 36.1 years, mean eGFR 80.9 ml/min/1/73m^2
- Metabolically healthy: HOMA-IR <2.5, absence of any components of the metabolic syndrome
- Incident CKD defined as eGFR <60 ml/min/1.73m^2

ChangY, et al. Ann Intern Med 2016. doi 10.7326/MIS-1323

Metabolically Healthy Obesity: Development of Chronic Kidney Disease

- n = 369,088 patient years of follow-up
- n = 906 incident cases of CKD
- Multi-variable adjusted differences in 5 year cumulative incidence of CKD compared with normal weight participants:

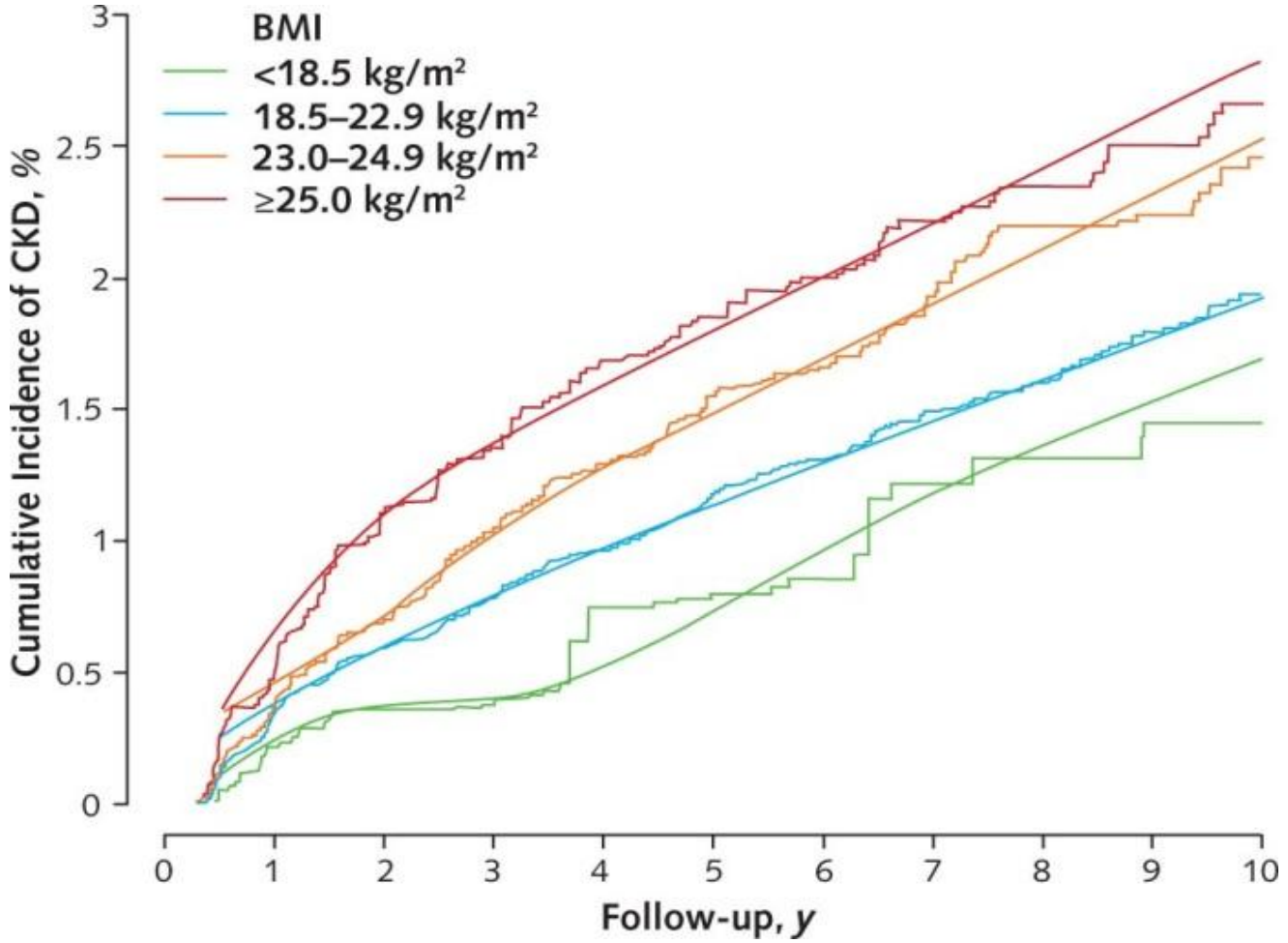
  underweight BMI (<18 kg/m^2) – 4.0 (-7.8 to -0.3)

  Overweight BMI (23.0 -24.9 kg/m^2) 3.5 (0.9 to 6.1)

  Obese BMI (>25.0 kg/m^2) 6.7 (3.0 to 10.6)

ChangY, et al. Ann Intern Med 2016. doi 10.7326/MIS-1323

Adjusted cumulative incidence of CKD, by BMI category at baseline, among metabolically healthy participants in the Kangbuk Samsung Health Study, 2002-2009 to 2013



ChangY, et al. Ann Intern Med 2016. doi 10.7326/MIS-1323

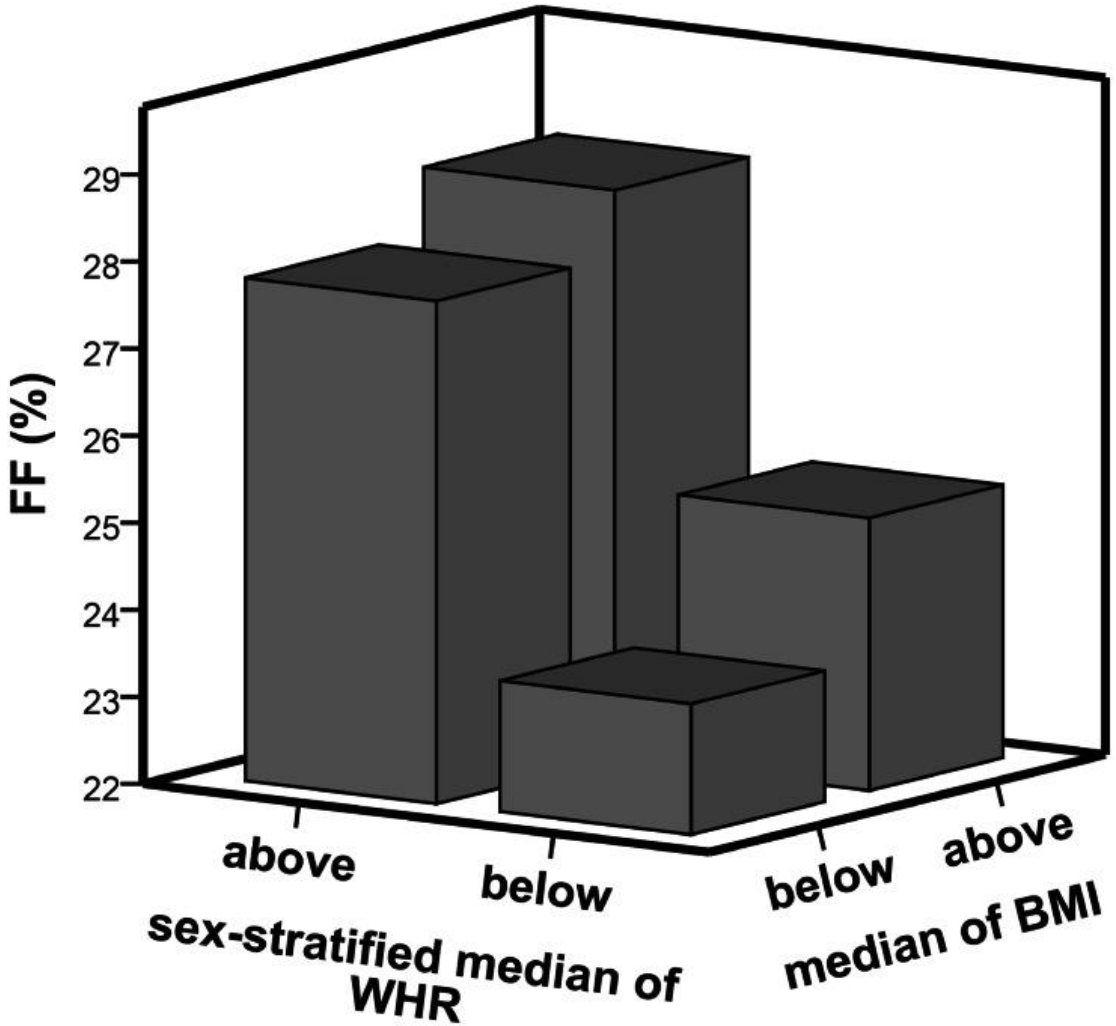
Pathophysiology Pathways of Obesity-related CKD

- Role of adipokine imbalance
- Obesity-related glomerulopathy
- Role of insulin resistance
- Role of lipid toxicity
- SNS and RAAS over activity
- Local adipose tissue RAAS
- Role of sleep-disordered breathing
- Role of fructose-rich diet
- Role of altered gut microbiota and chronic inflammation

Central Body Fat Distribution

- Increased glomerular hypertension
- Glomerular hypertrophy
- Decreased podocyte density
- Increased foot processes

Mean FF per median WHR and BMI. Three-dimensional bar graph showing the combined effects of WHR and BMI on FF, with mean FF (y-axis) per sex-stratified median of WHR (x-axis) and median BMI (z-axis). Median WHR was 0.86 and median BMI was 24.6 kg/m2



Arjan J. Kwakernaak et al. JASN 2013;24:987-994.

These alterations promote proteinuria and glomerulosclerosis!

Obesity Affects Adipokines

- Reduced adiponectin
- Adiponectin inversely related to albuminuria
- Administration of adiponectin reduces podocyte permeability to albumin, and reduces podocyte dysfunction

Obesity Affects Leptin

- Increased leptin levels
- Infusion of leptin increases proteinuria, glomerulosclerosis
- Promotes renal fibrosis, oxidative stress and SNS activity

Do energy dense foods with a high glycemic index increase the risk of obesity-related CKD?

High fructose syrup causes:

-incident hypertension

-increased uric acid

-increased BP salt sensitivity

-increased gout, HTN, T2DM

Novel Hypotheses Linking Obesity and CKD

- Mutation of the uricase gene
- Micro RNAs
- Altered gut microbiota
- Neurocognitive factors

Obesity and Kidney Health

- The project was an observational, one-sample, two-sample Mendelian randomization (MR) and multivariable MR studies in ~300 000 participants of white-British ancestry from UK Biobank and participants of predominantly European ancestry from genome-wide association studies.
- The MR analyses revealed that increasing values of genetically predicted body mass index and waist circumference were causally associated with biochemical indices of renal function, kidney health index (a composite renal outcome derived from blood biochemistry, urine analysis, and International Classification of Disease-based kidney disease diagnoses), and both acute and chronic kidney diseases of different etiologies including hypertensive renal disease and diabetic nephropathy.

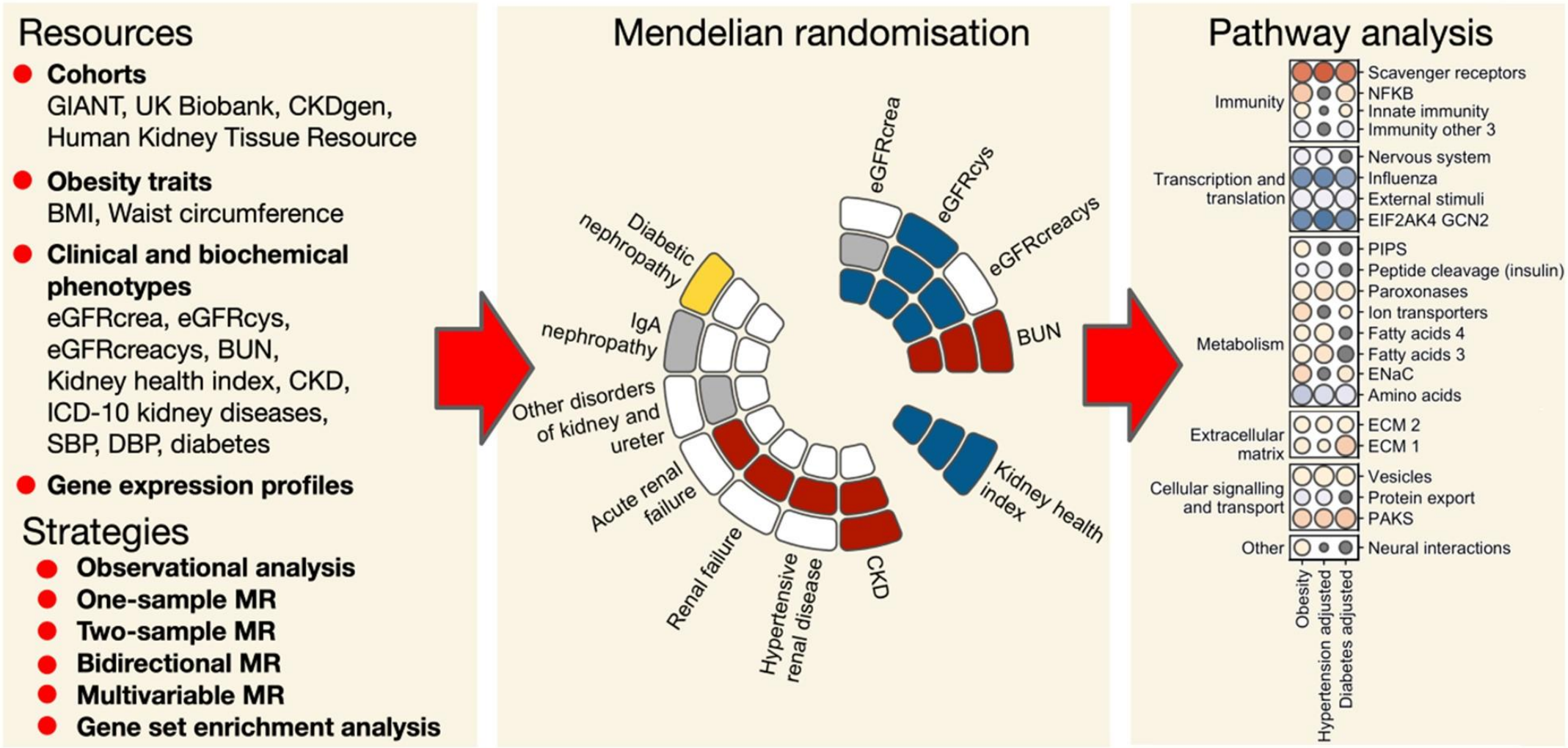
Obesity and Kidney Health

- Approximately 13–16% and 21–26% of the potentially causal effect of obesity indices on kidney health were mediated by blood pressure and type 2 diabetes, respectively.
- A total of 61 pathways mapping primarily onto transcriptional/translational regulation, innate and adaptive immunity, and extracellular matrix and metabolism were associated with obesity measures in gene set enrichment analysis in up to 467 kidney transcriptomes.

Obesity and Kidney Health

- The data show that a putatively causal association of obesity with renal health is largely independent of blood pressure and type 2 diabetes and uncover the signatures of obesity on the transcriptome of human kidney.

GRAPHICAL ABSTRACT



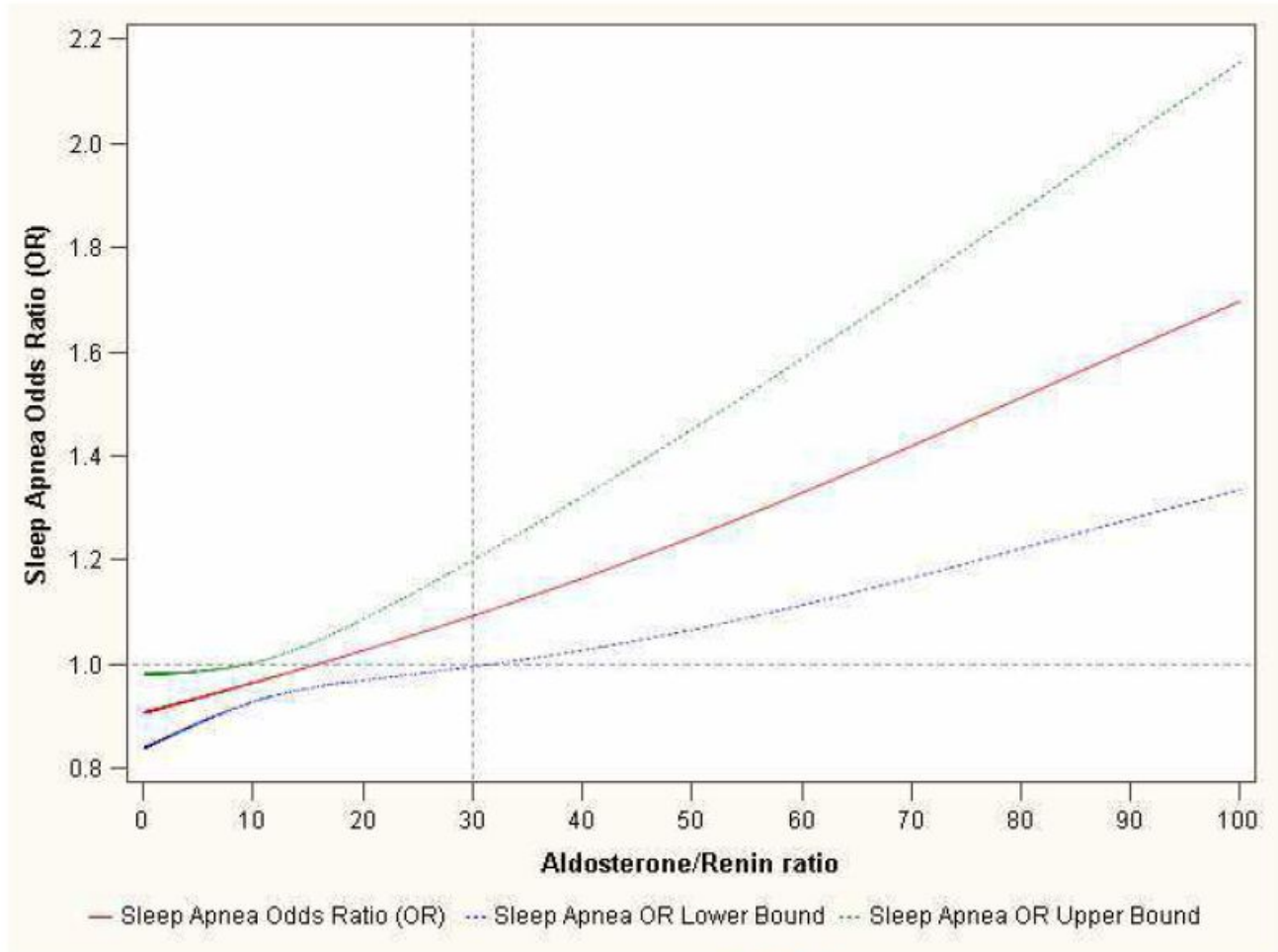
Cardiovasc Res, cvab357, https://doi.org/10.1093/cvr/cvab357

What about obesity and aldosterone?

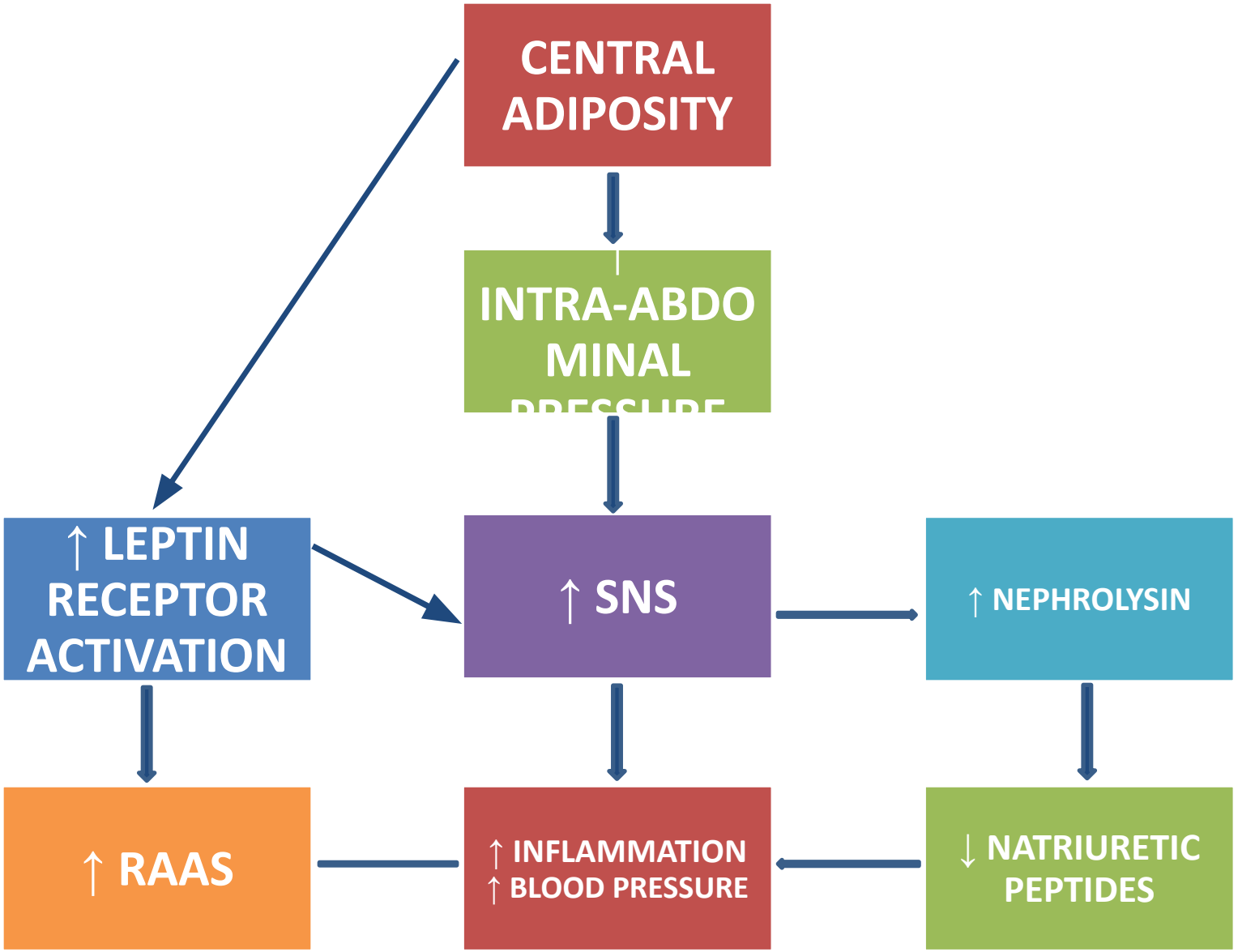
Not much written about it.

But, …

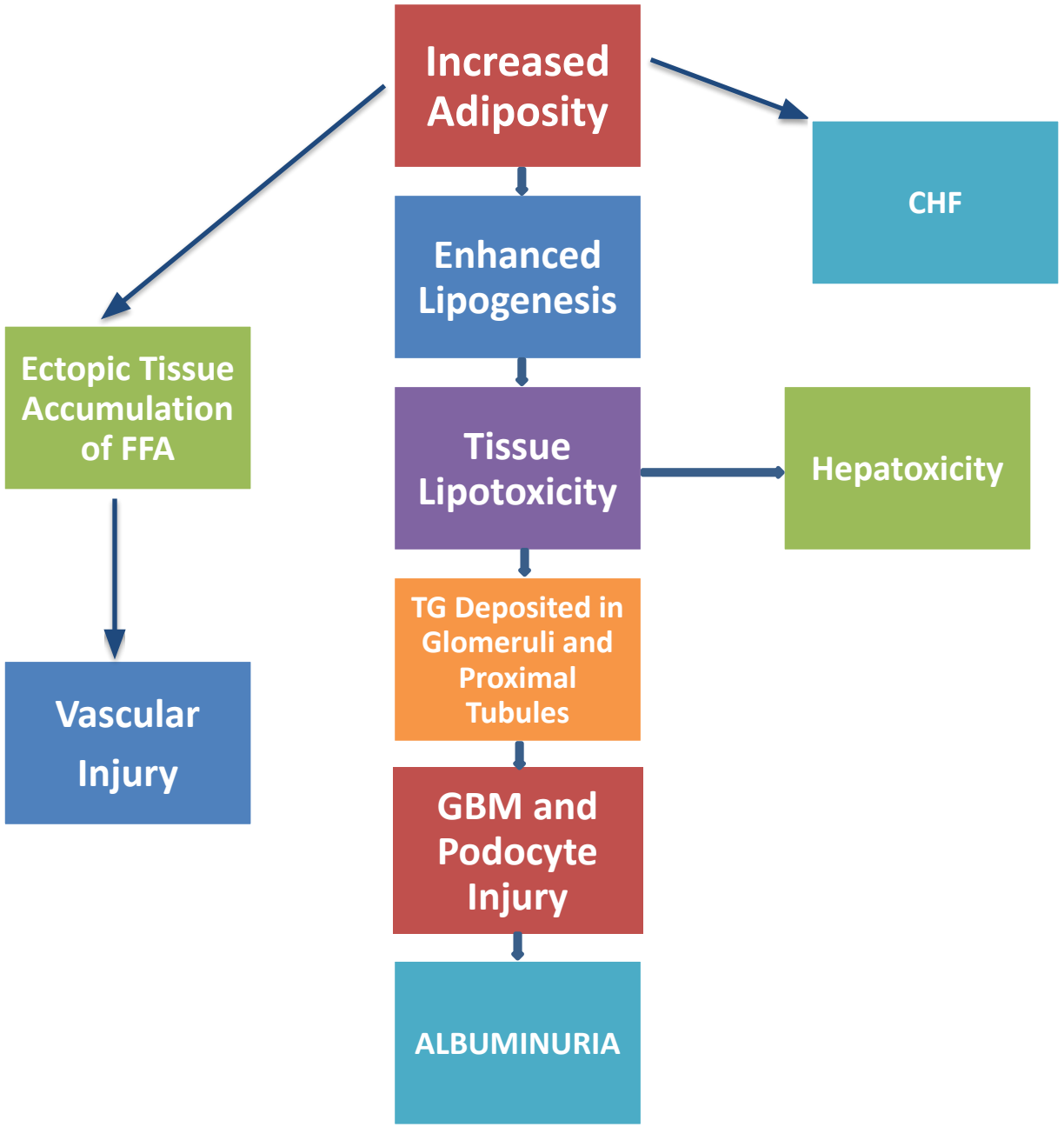
Positive Relationship of Sleep Apnea to Hyperaldosteronism in an Ethnically Diverse Population



SNS and RAAS Over-Activity



Lipid Toxicity and CVD and CKD



Local Adipose Tissue RAAS

- Some Adipokines are mineralocorticoid – releasing factors
- Aldosterone synthesis in adipocytes
- Leptin associated with increased aldosterone synthase, and aldosterone levels

Adipocyte-driven hyperaldosteronism enhances a pro-inflammatory state, insulin resistance oxidative stress, renal tubular Na reabsorption, and salt sensitive hypertension.

Sowers JR, et al. Ann Intern Med 2009. 150:776-783.
Bogaert YE, Linas S. Nat Clin Pract Nephrol. 2009 Feb;5(2):101-11.

Association between Fatty Liver Index and CKD: the population-based KORA study

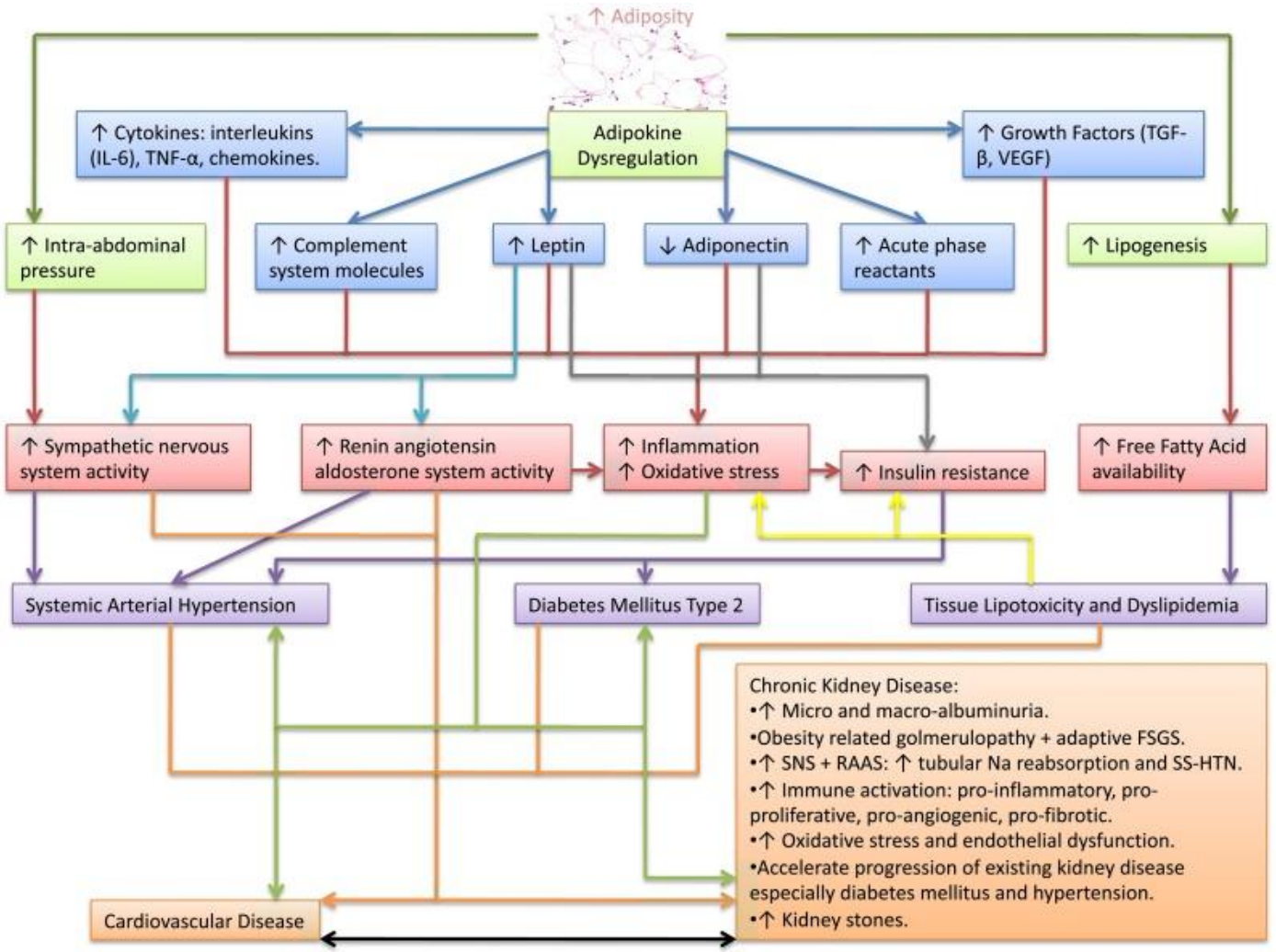
- n= 2920 participants
- Followed for 6.5 years
- The prevalence of fatty liver was 40.4% and CKD 5.6% at baseline
- Fatty liver index was inversely associated with eGFR
- Mediation analysis showed that the association was completely mediated by inflammation, diabetes, and hypertension

Cai X, et al. Nephrol Dial Transplant 2022 (In press)

Role of Altered Gut Microbiota and Chronic Inflammation in Obesity and CKD

- Complex, not fully educated
- Altered gut microbiota
- Leaky gut syndrome
- Endotoxemia
- Inflammatory State

Many of the multiple mechanisms and interactions that can lead to the development of chronic kidney disease and cardiovascular disease



Lakkis, J, Weir, MR. Progressive Cardiovascular Diseases 51 (2018) 157-167.

Treatment of Obesity in CKD

- Not much data
- Some is conflicting
- Not enough large prospective studies
- Who are the best types of patients to study? Early disease? Late disease?

Available Evidence

- Low calorie diets associated with improved GFR and albuminuria
- Lower sodium diet with less glomerular hyperfiltration in overweight subjects
- Adherence to healthy life style associated with lower all cause mortality in patients with CKD.
- Sedentary lifestyle associated with prevalent CKD

Pharmacological Treatment

- ACE inhibition reduced the rate of renal events in obese patients with CKD more effectively than non-obese patients
- Mineralocorticoid receptor blockade
- SGLT2 Inhibition
- GLP-1 receptor agonist

Bariatric Surgery Treatment

- Small studies, often not controlled
- Less albuminuria
- Less hypertension
- Less measures of inflammation

Conclusions

- Increased fat mass promotes kidney disease through both direct and indirect mechanisms
- The major direct mechanisms are hypertension / diabetes / atherosclerosis
- The major indirect mechanisms are vasculotoxicity via aldosterone, RAS and SNS activation, oxidative stress, inflammation, less adiponectin and more leptin

Conclusions

- Increased central fat mass associated with glomerular capillary hypertension, albuminuria and glomerulosclerosis!