The aging kidney – pathophysiology and therapeutic consequences

Jan T. Kielstein

Department of Nephrology and Hypertension

Medical School Hannover

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1. Demographic changes
2. Incidence of CKD
3. Measurement of renal function
4. Pathophysiology
5. Practical considerations

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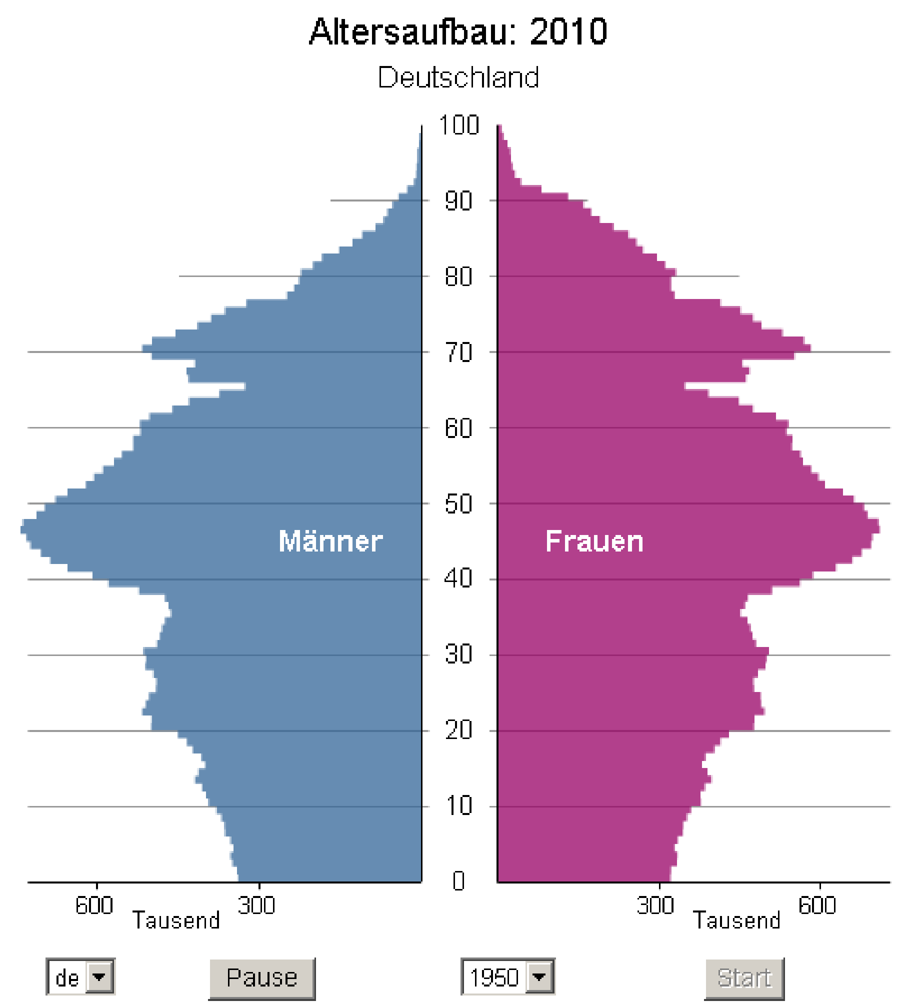
Demographics in Germany 2010

http://www.destatis.de



DESTATIS wissen.nutzen.

12. koordinierte Bevölkerungsvorausberechnung

1950 bis 2008: Fortschreibung
2009 bis 2060: Vorausberechnung

Variante 1-W1 Die Annahmen:

- Geburtenhäufigkeit annähernd konstant bei 1,4 Kindern je Frau
- Lebenserwartung Neugeborener im Jahr 2060: 85,0 Jahre für Jungen 89,2 Jahre für Mädchen
- Jährlicher Wanderungssaldo + 100 000 Personen

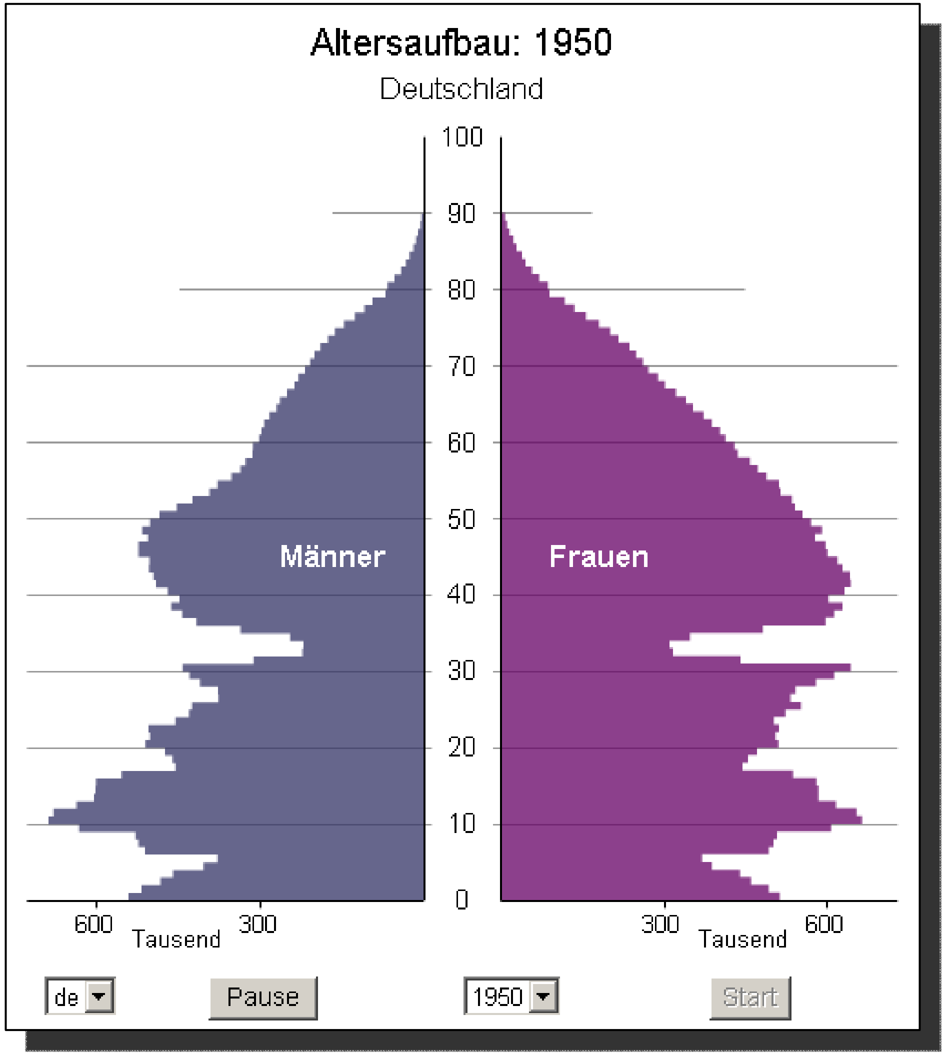
Altersgruppen

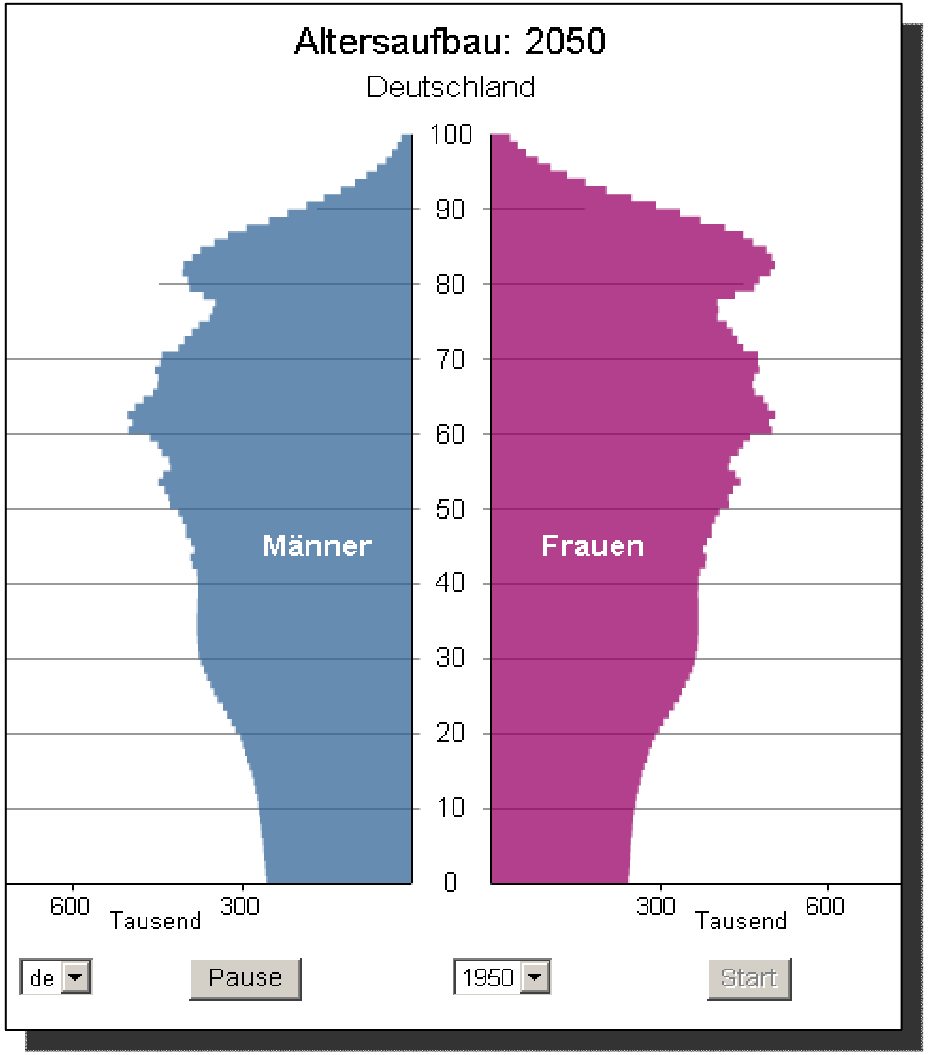
<20	20–64	65+	Gesamt		AQ
14.8	49.7	16.8	81.4	Mill.	34
18	61	21	100	%	

☐ Altersgruppen ändern
☐ Frauen- bzw. Männer-Überschuss anzeigen

1950 - 10 % of the population > 65 Jahre
2050 - 33 % of the population > 65 Jahre

http://www.destatis.de





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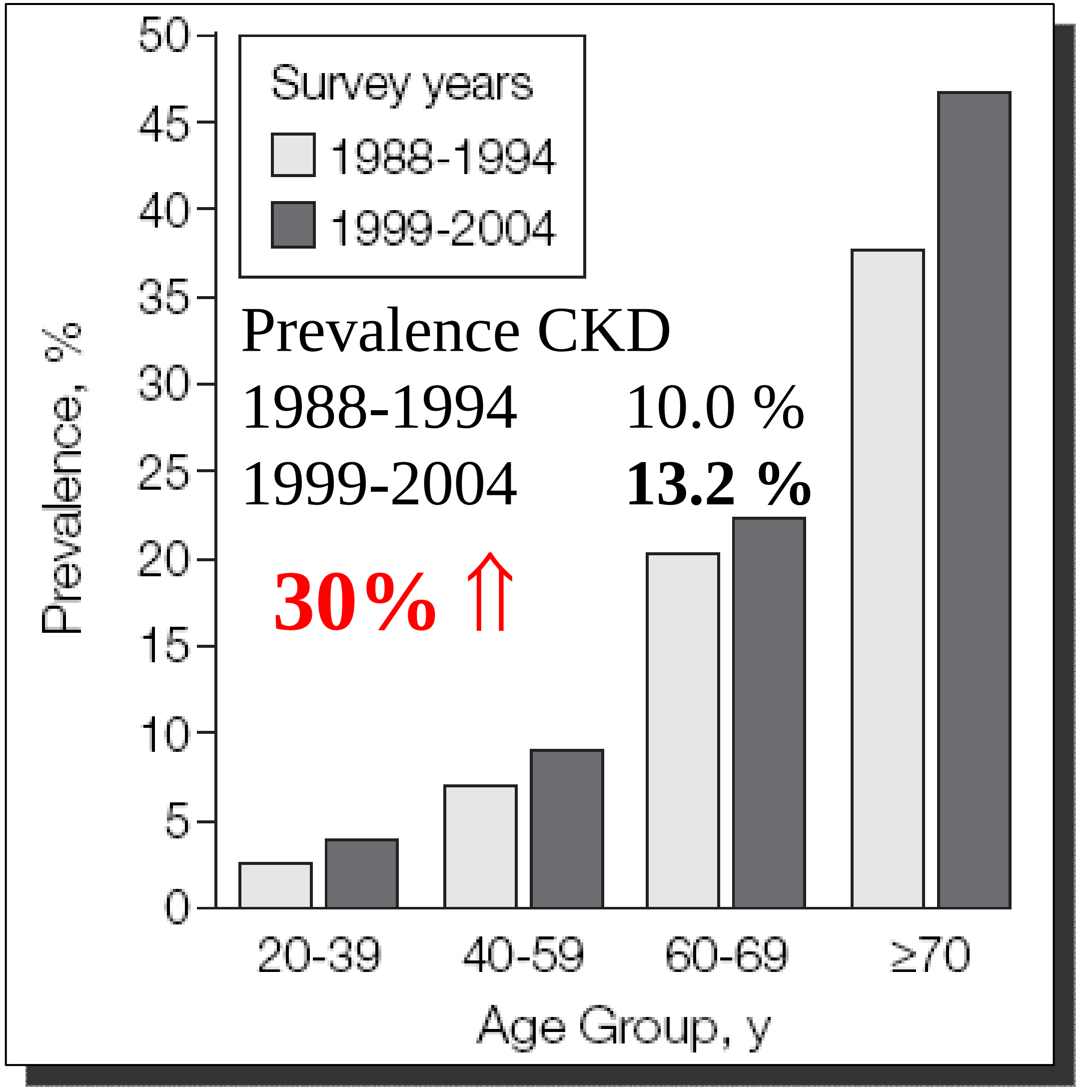
Prevalence of Chronic Kidney Disease (CKD) Stages in US Adults Aged 20 Years or Older Based on NHANES 1988-1994 and NHANES 1999-2004

CORESH et al. *JAMA* 298: 2038 – 2047, 2007



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Where did the paradigm of decline in renal function with age come from?

- **drop in GFR: ~ *10 ml/min/1.73m² / decade* after the age of 40 (~ *1 ml/min/1.73m² per year)***
- **drop in ERPF: ~ *80 ml/min/1.73m² decade* after the age of 40**

Age changes in glomerular filtration rate, effective renal plasma flow and tubular excretory capacity in adult males

DAVIES & SHOCK *J Clin Invest* 29: 1950-1955, 1950

AGE CHANGES IN GLOMERULAR FILTRATION RATE, EFFECTIVE RENAL PLASMA FLOW, AND TUBULAR EXCRETORY CAPACITY IN ADULT MALES

BY DEAN F. DAVIES [1] AND NATHAN W. SHOCK

(From the National Heart Institute, National Institutes of Health, Bethesda, Maryland; and the Gerontology Section, Baltimore City Hospitals, Baltimore)

(Submitted for publication October 25, 1949; accepted, December 28, 1949)

It has previously been shown that inulin clearance, diodrast clearance, and diodrast Tm are significantly lower in males between the ages of 60 and 80 years than in males 20–40 years of age (1, 2). The clearance and Tm values commonly used as norms are based on averages calculated from observations made on subjects between the ages of 17 and 68 years (3–5).

The present study was undertaken to evaluate the rate of the age changes in renal functions previously reported.

milk or fruit was permitted in addition to water. Subjects were hydrated for one to two hours before the test with 600 to 800 cc. of water, and 200 cc. of water was given at half-hourly intervals during the test. Blood pressure was taken after the subject had been resting in bed at least one-half hour in a semi-reclining position with the head gatch at 15 to 30 degrees. This elevation was maintained throughout the test. Infusion of fluid during equilibration, clearance, and Tm periods was regulated accurately at 3.0 cc./min. with a tunnel clamp. Four clearance and four Tm periods of 10 to 14 minutes each were taken according to the method of Smith and associates (5). Blood samples were drawn at the mid-point of each pe-

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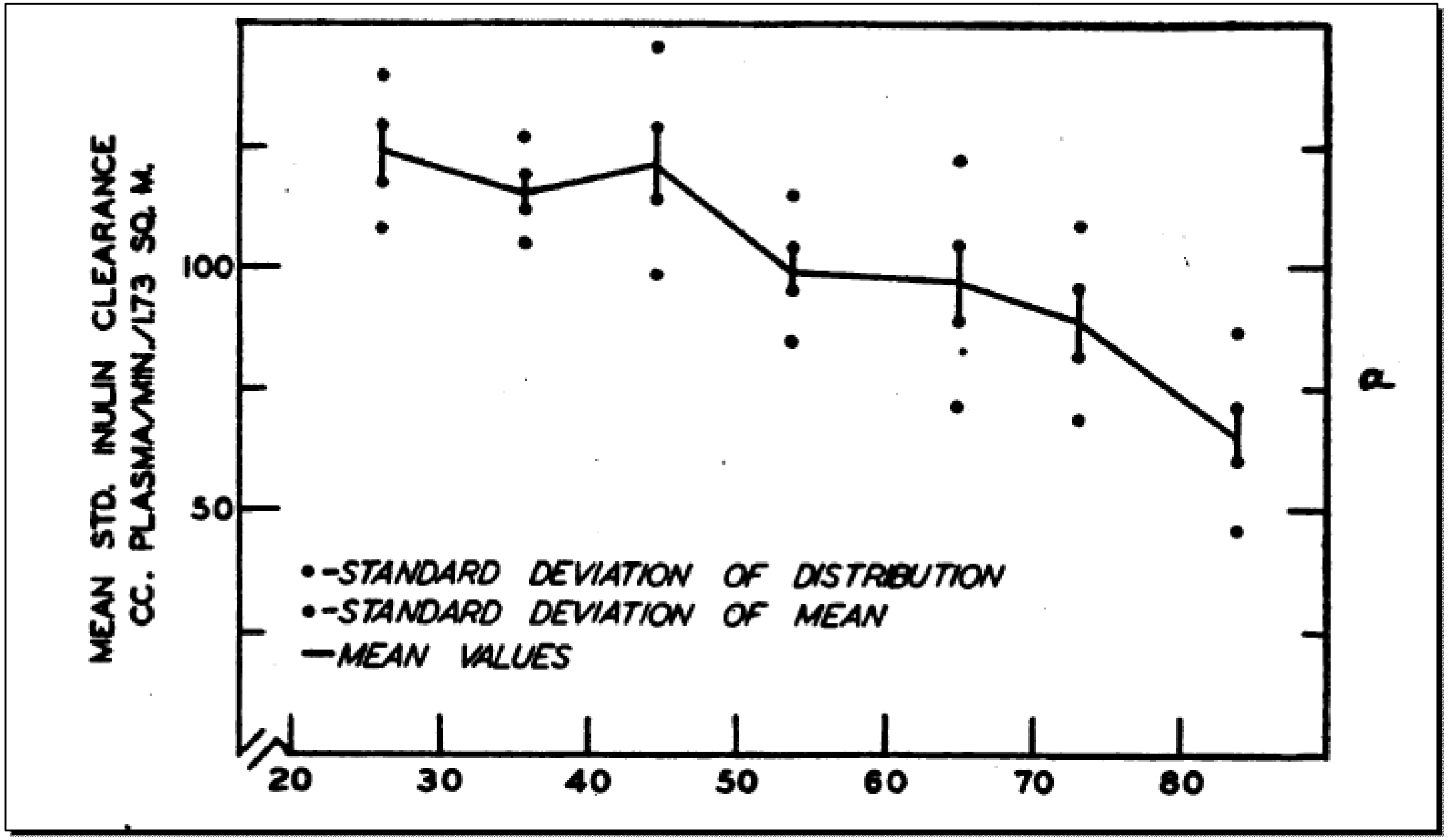
DAVIES & SHOCK *J Clin Invest* 29: 1950-1955, 1950



The average inulin clearance dropped from 122.8 to 65.3 cc./min./1.73 sq.m. between the ages of 20 and 90 (46 %).

MHH Medizinische Hochschule Hannover

Age changes in glomerular filtration rate, effective renal plasma flow and tubular excretory capacity in adult males

DAVIES & SHOCK *J Clin Invest* 29: 1950-1955, 1950

60–69 year age group			
4*	61	110/70	Pyohydronephrosis with bilateral hydroureter.
31*	69	160/98	Hydrarthrosis; arthritis of knee.
58	62	150/85	Blindness, rt. eye, due to methyl alcohol.
60	66	130/76	Healed duodenal ulcer; fracture of shaft of radius and valve with union.
62	64	—	Traumatic spastic paraplegia.
72	65	130/90	Post-traumatic cortical atrophy.
110	66	—	Varicose veins.
112	62	110/72	Syphilis of undiagnosed site; osteoarthritis.
114	67	140/90	Generalized arteriosclerosis; cerebral arteriosclerosis.
120	68	160/80	Bilateral indirect inguinal hernia; benign prostatic hypertrophy.‡
70–79 year age group			
13*	77	104/60	Chronic bronchitis; generalized arteriosclerosis; benign prostatic hypertrophy. Hydronephrosis,§ bilateral.
15*	70	—	Intestinal obstruction; carcinoma of rectum.
25*	72	—	Central nervous system syphilis.
89	72	130/75	Generalized arteriosclerosis; anophthalmus, rt. eye; tuberculosis of lungs.
141	78	128/62	Generalized arteriosclerosis; senile emphysema.
143	71	140/90	Generalized arteriosclerosis.
144	74	162/90	Vocal cord paralysis.
153	71	120/65	Amputated left leg mid-thigh; chronic infected ulcerated area on rt. leg due to old injury.
200	71	112/58	Chronic bronchiectasis; hypertrophic arthritis of spine.

Age changes in glomerular filtration rate, effective renal plasma flow and tubular excretory capacity in adult males

DAVIES & SHOCK *J Clin Invest* 29: 1950-1955, 1950

80–89 year age group

17	80	110/70	Generalized arteriosclerosis; carcinoma of stomach with metastasis to liver.‖
48	80	140/70	Calcification of aortic valve; hypertrophic arthritis; senile emphysema.
52	87	150/80	Coronary artery disease; generalized arteriosclerosis; narrowing of coronary arteries; cardiac hypertrophy, mild.
54	86	114/74	Arteriosclerosis; squamous cell carcinoma of neck.
59	86	170/85	Squamous cell carcinoma of lower lip; generalized arteriosclerosis.
61	80	144/72	Dorsal kyphosis; otosclerosis; deafness.
63	80	182/82–70	Comminuted simple fracture, femur; amputation rt. leg.
69	85	—	Chronic arthritis.
70	87	—	Generalized arteriosclerosis; arthritis, left knee.
84	81	150/64	Generalized arteriosclerosis; tuberculosis; compensatory emphysema; inactive tuberculosis of lungs.
88	83	120/75	Generalized arteriosclerosis; benign prostatic hypertrophy.
91	89	130/84	Pulmonary emphysema; benign prostatic hypertrophy; emaciation, marked.

* From original series previously published.
† No cardiac enlargement; 120/80 on physical examination for test.
‡ Discovered at autopsy two years after function test.
§ Discovered at autopsy three years after function test.
‖ Discovered at autopsy 14 months after function test.

Nierenfunktion im Alter: Physiologie und Pathophysiologie

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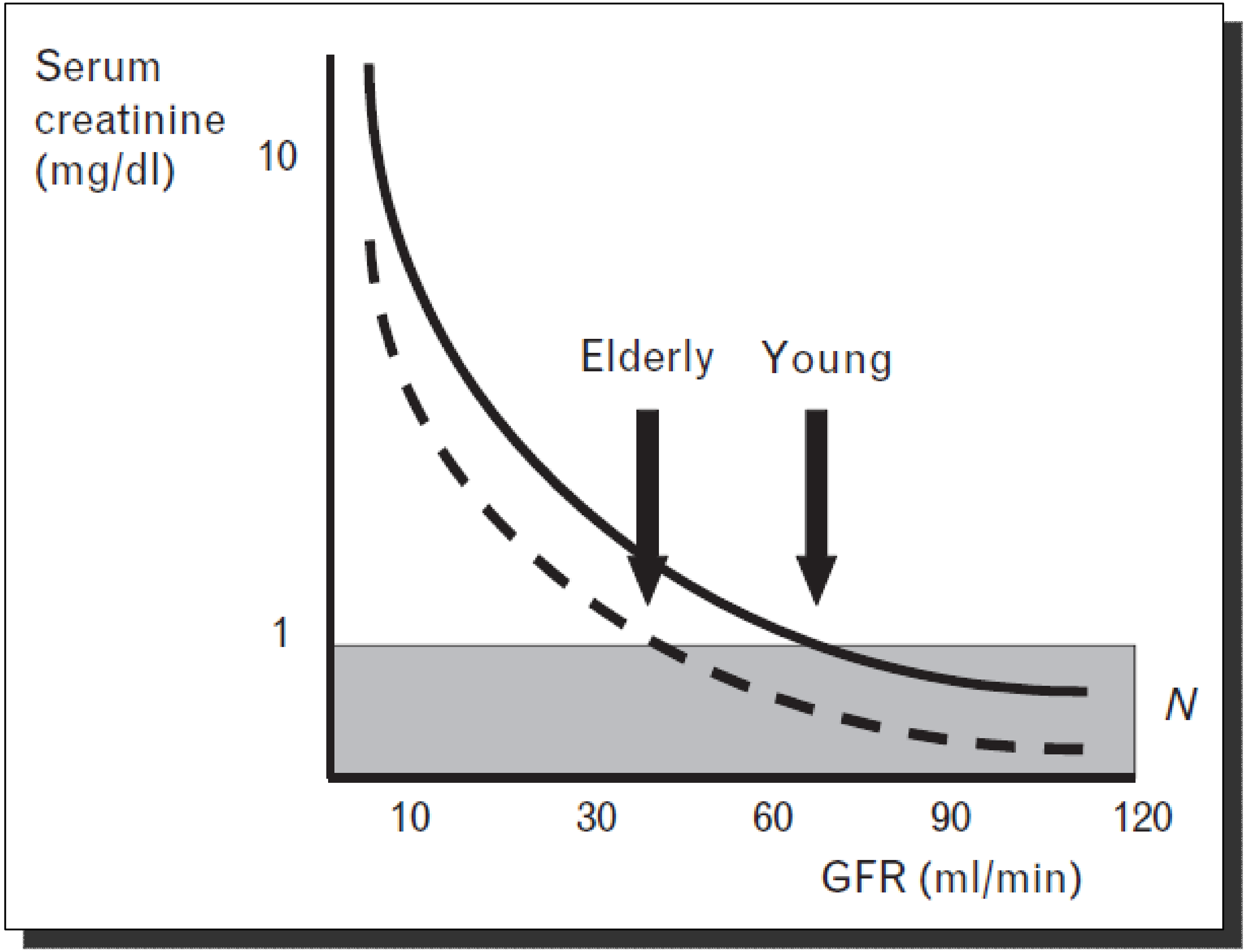
Assessment of renal function in elderly patients

FLISER *Current Opinion in Nephrology and Hypertension* 17:604–608, 2008



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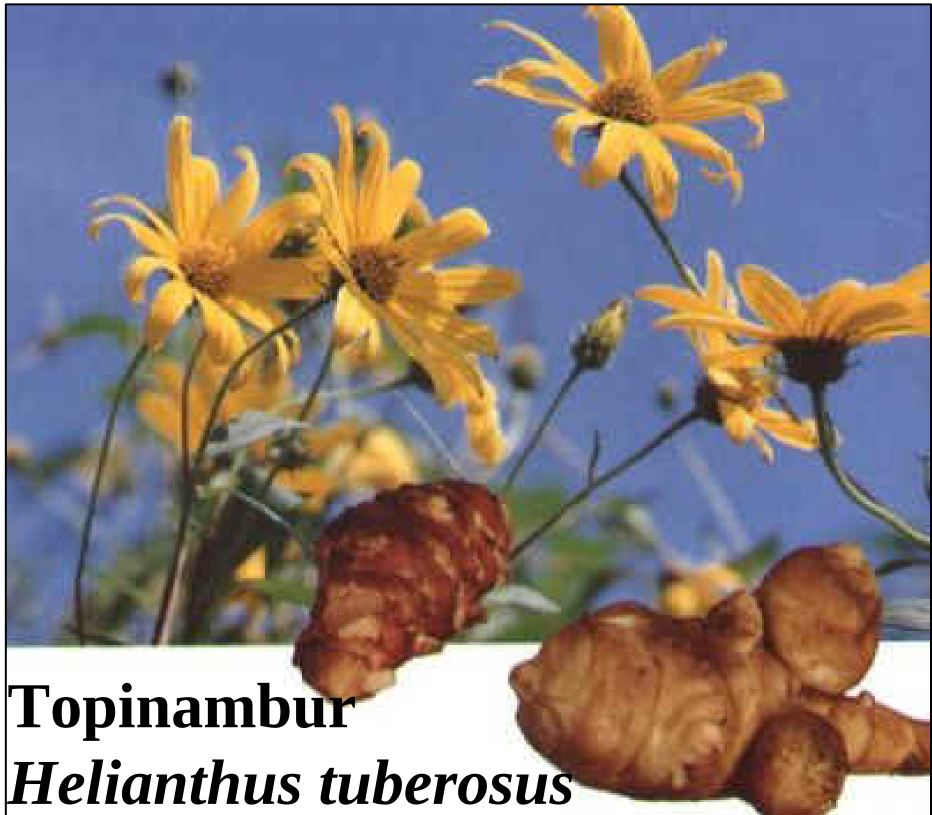
How to determine renal function

Inulin clearance



Topinambur
Helianthus tuberosus

- **Inulinclearance – gold standard**
- **100 % glomerular filtration**
- **neither tubular secretion nor tubular adsorbtion**
- **no metabolism**

How to determine renal function

Creatinine clearance

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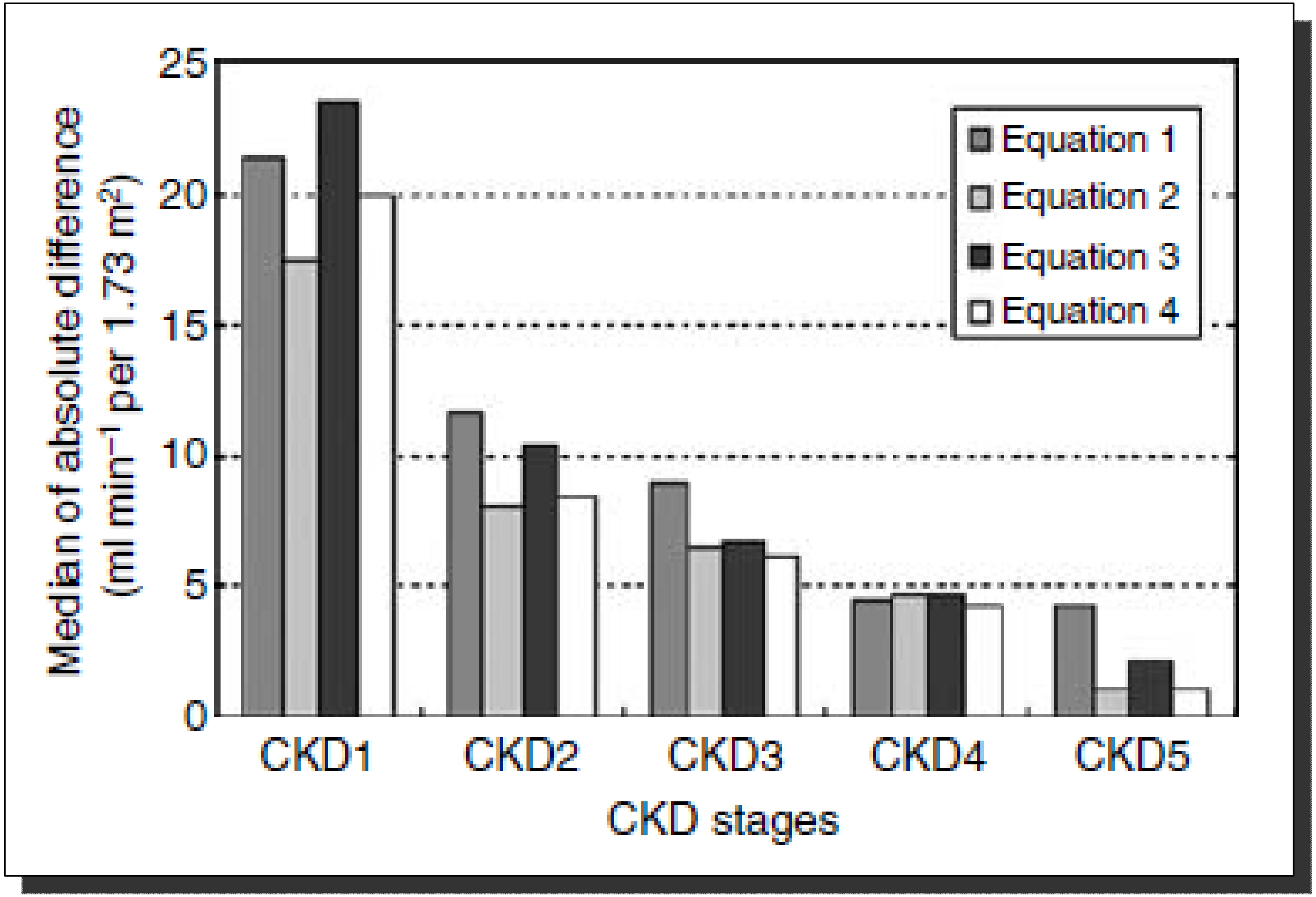
How to determine renal function

Cockroft-Gault

Cockcroft-Gault Calculator (with SI Units)	
Plasma creatinine (PCR) ○ mg/dL ◉ umol/L	95
Weight (wt) ◉ kilograms ○ pounds	55
Gender	○ Male ◉ Female
Age	62
GFR value	**47.2 ccs/min**

Improved GFR estimation by combined creatinine and cystatin C measurements.

MA et al. *Kidney Int* 2007; 72:1535–1542, 2007



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How to determine renal function

MDRD Formula

$$\text{GFR (ml/min/1,73 m}^2\text{)} =$$

$$186 \times (\text{S-Kreatinin})^{-1{,}154} \times (\text{Alter})^{-0{,}203} \times 0{,}742\ (\text{F})$$

MDRD GFR Calculator (with SI Units)

by Stephen Z. Fadem, M.D., FACP, FASN

Plasma creatinine ○ mg/dL ⦿ umol/L	79
Age	88
Race	○ African American ⦿ White*
Gender	○ Male ⦿ Female
GFR value:	63 ml/min/1.73 m^2 in white* females

(Age, Race, Gender
Plasma creatinine)

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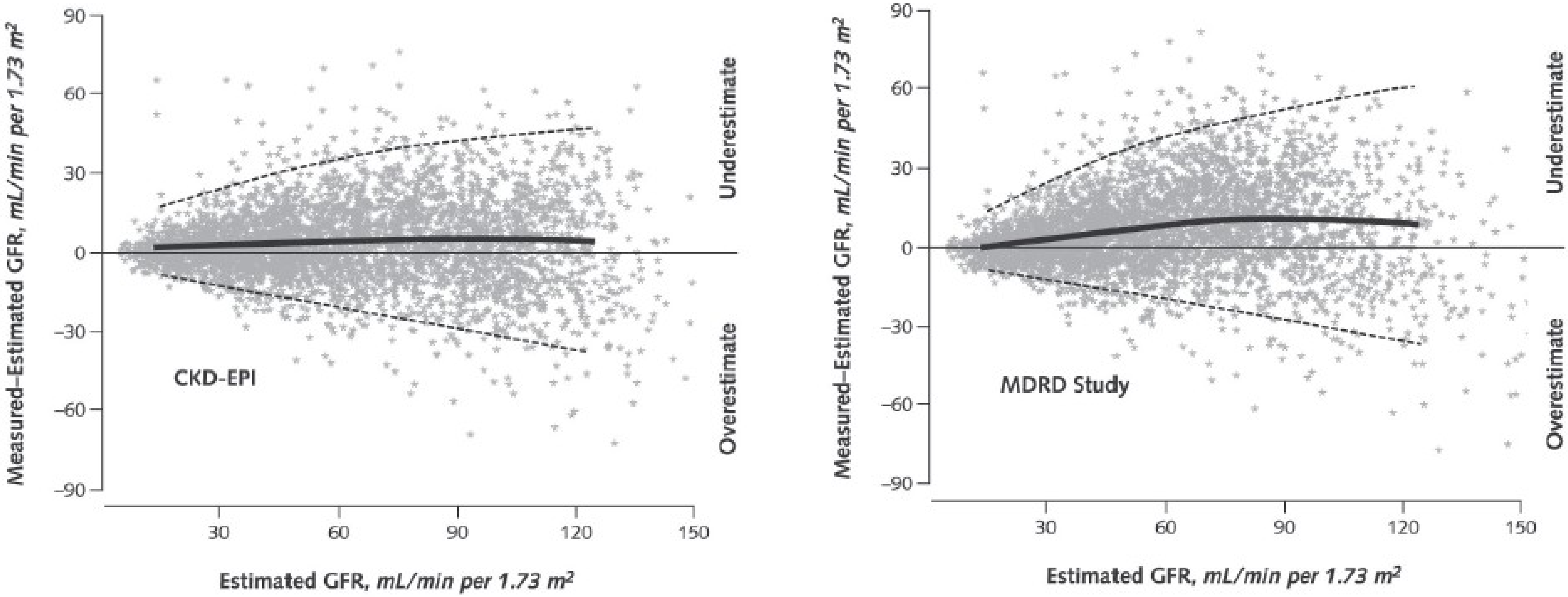
A New Equation to Estimate Glomerular Filtration Rate

LEVEY et al. *Ann Intern Med.* 150:604-612, 2009

Figure. Performance of the CKD-EPI and MDRD Study equations in estimating measured GFR in the external validation data set.



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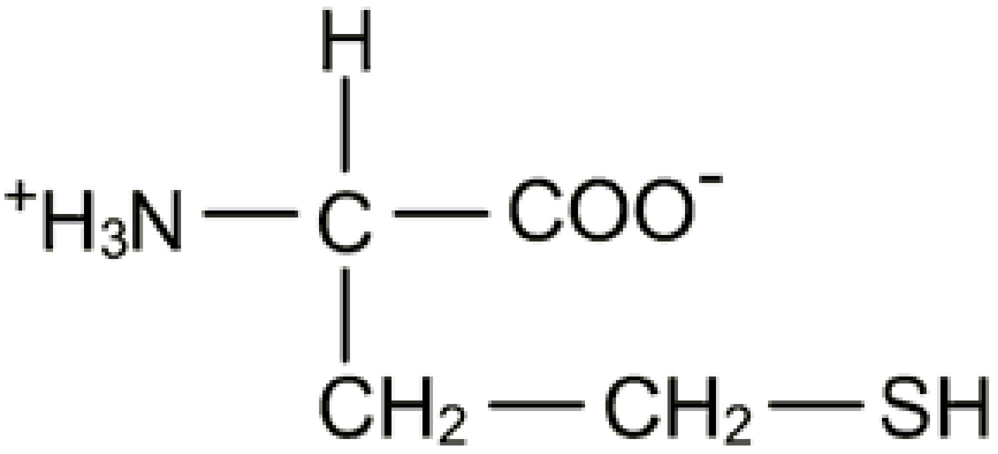
Vascular pathology of homocysteinemia: implications for the pathogenesis of arteriosclerosis

McCully *Am J Pathol* 56: 111-128, 01.07.1969

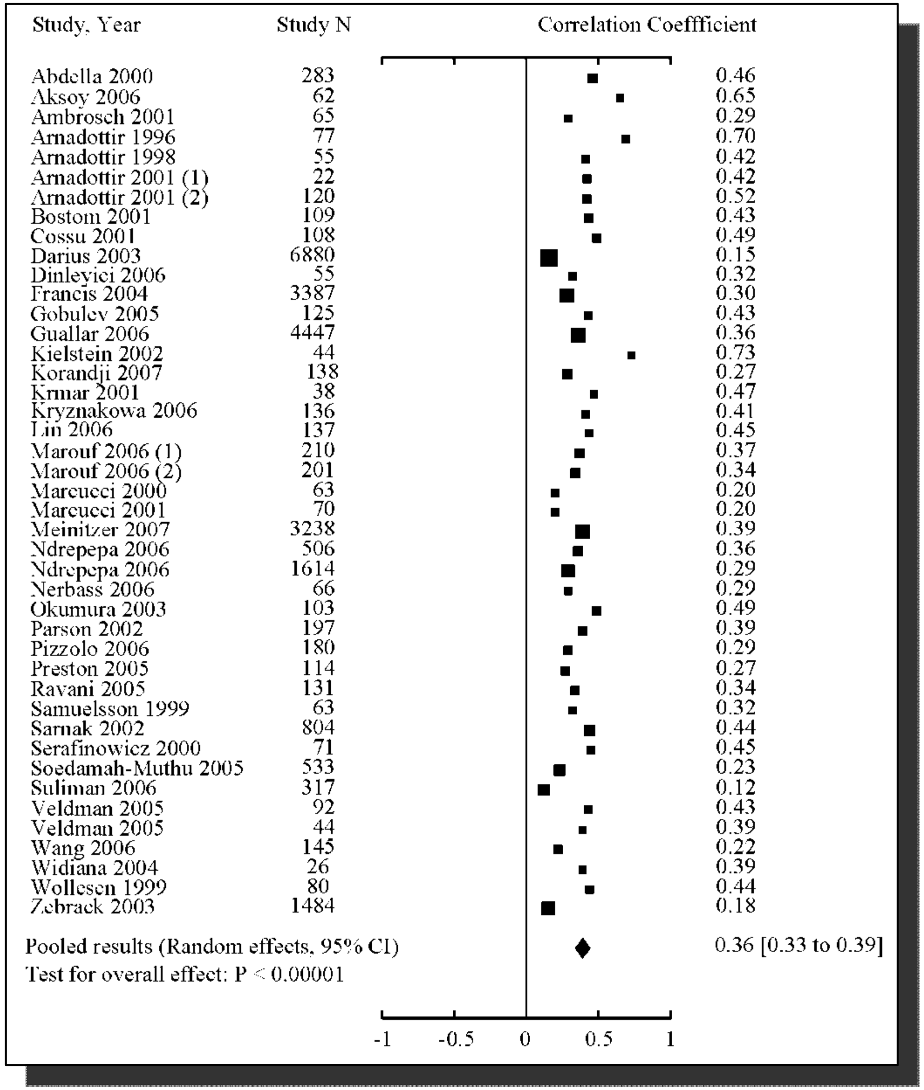


Homocysteine

Two cardiovascular risk factors in one? Homocysteine and its relation to glomerular filtration rate.

A meta-analysis of 41 studies with 27,000 participants

KIELSTEIN et al. *Kidney Blood Pres Res*, 31(4):259-67, 2008



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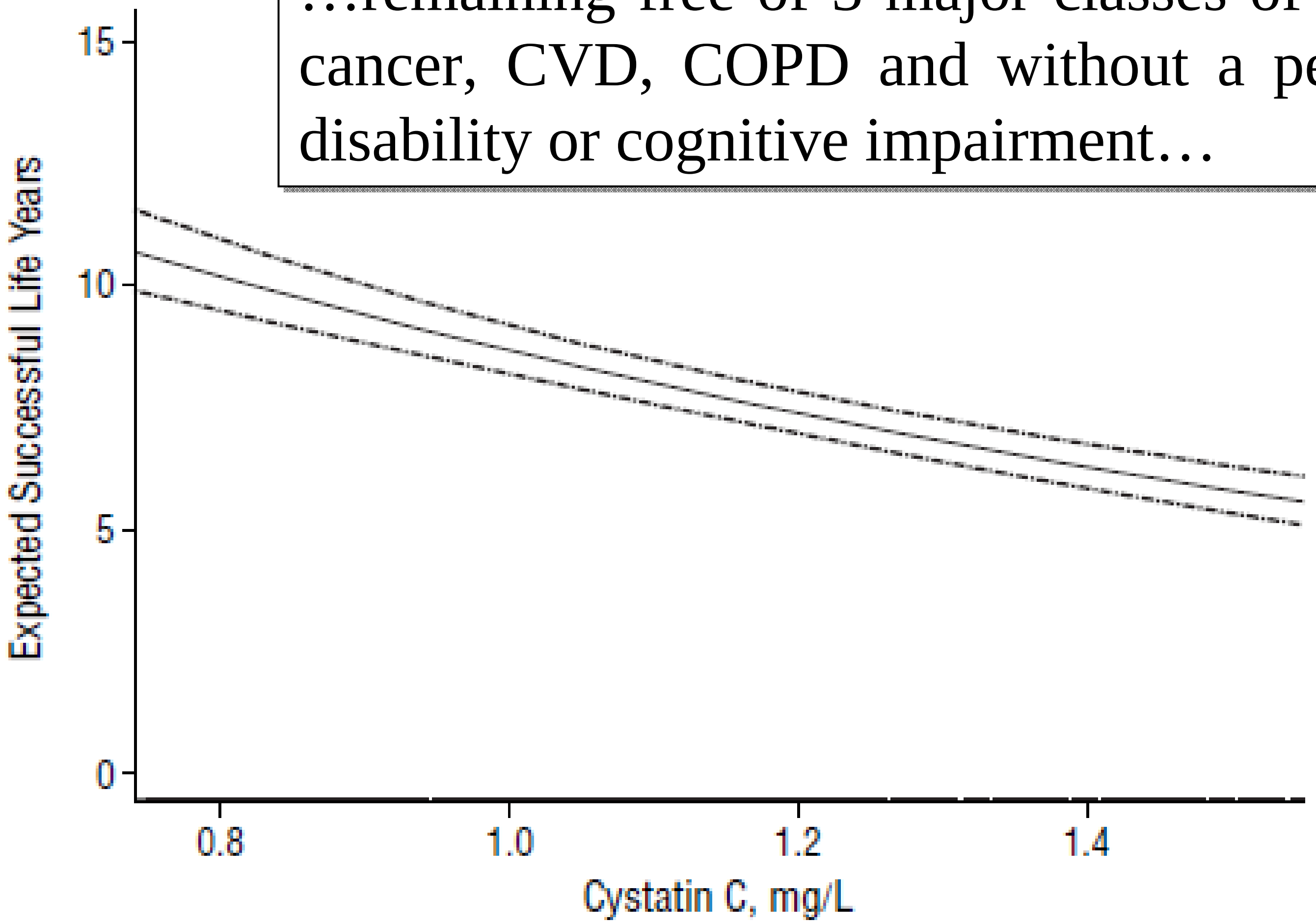
Cystatin C and Aging Success
n=2140, median follow up 5.2 years
SARNAK et al. *Arch Intern Med* 168:147–153, 2008

…remaining free of 3 major classes of disease (incident cancer, CVD, COPD and without a persistent physical disability or cognitive impairment…



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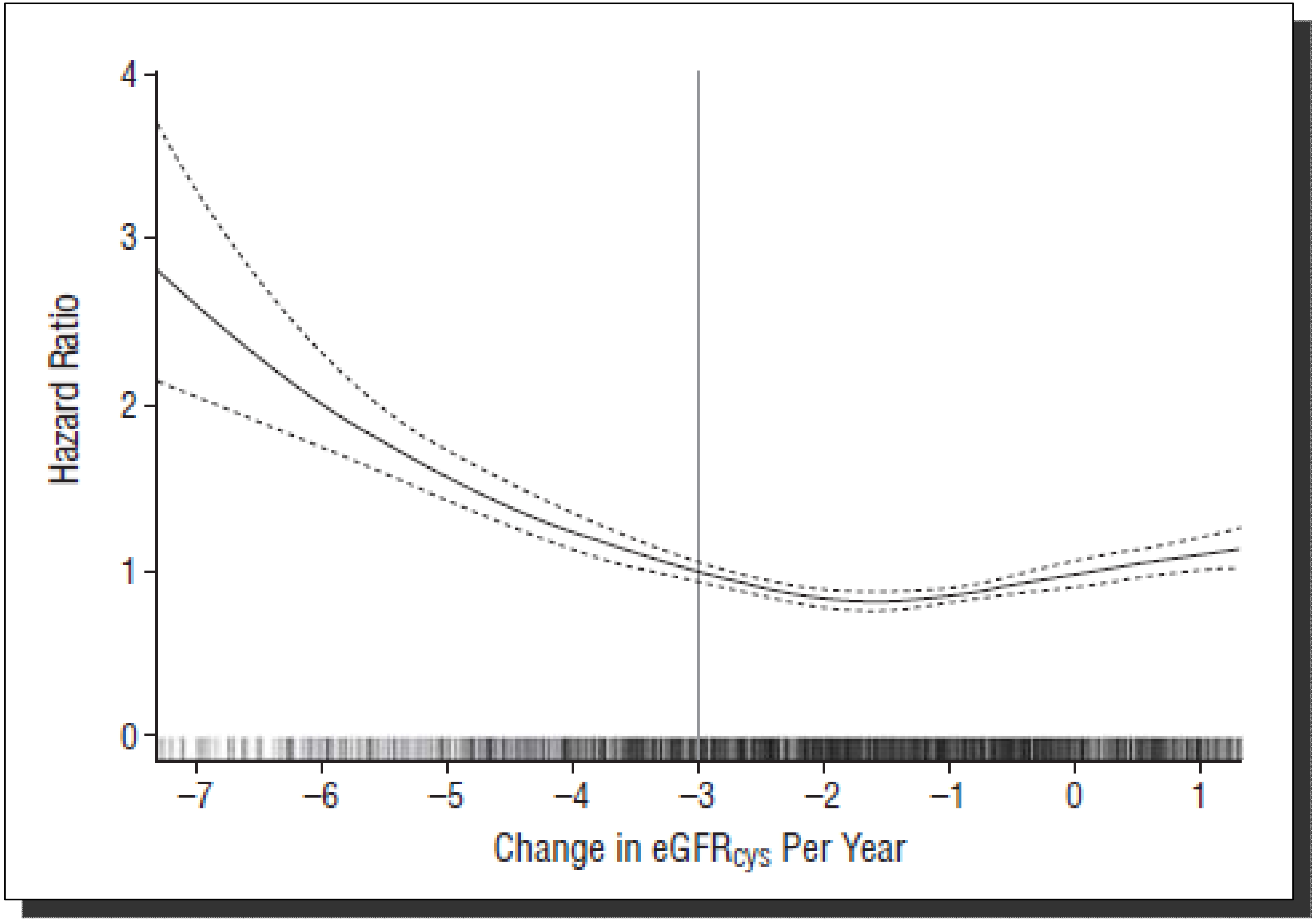
Rapid Kidney Function Decline and Mortality Risk in Older Adults

n=4380, median follow up 9.9 years

RIFKI et al. *Arch Intern Med* 168:2212-2218, 2008



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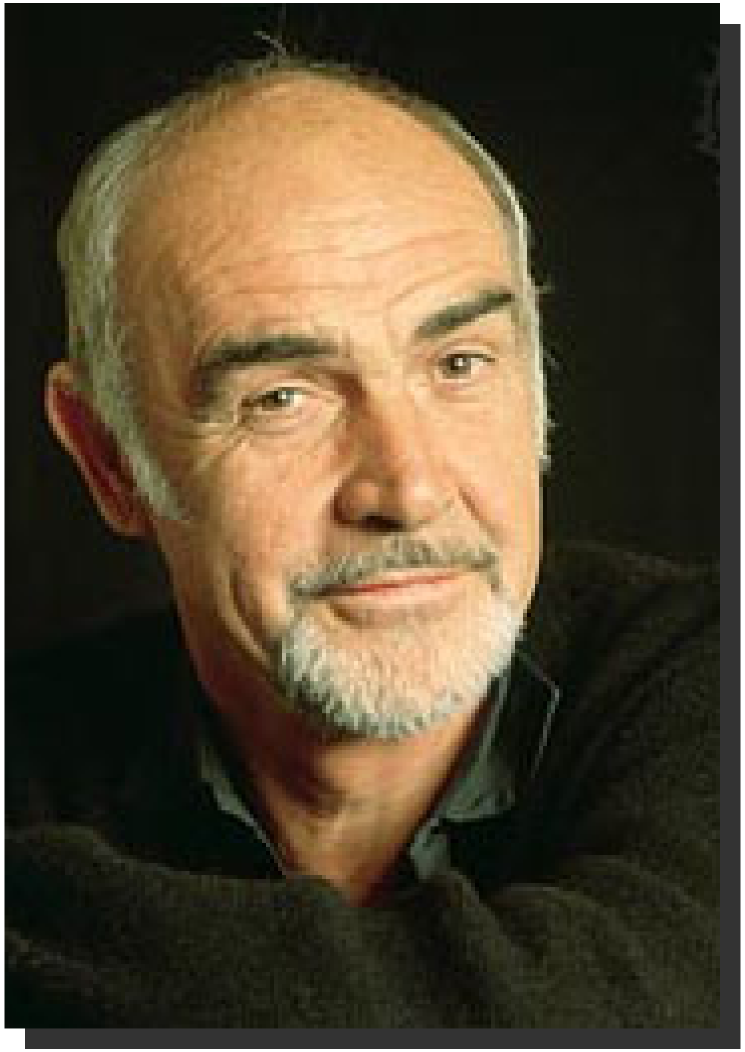

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FLISER *Current Opinion in Nephrology and Hypertension* 17:604–608, 2008

(1) Atherosclerosis.
(2) Hypertension/left ventricular dysfunction.
(3) Glucose intolerance/diabetes mellitus.
(4) Obesity.
(5) Heart failure.
(6) Undetected renal
(7) Smoking.
(8) Disabling diseases

Isolation and identification of ADMA and SDMA from human urine

KAKIMOTO & AKAZAWA *JBC* 245: 5752-5758, 1970

Isolation and Identification of N^G,N^G- and N^G,N'^G-Dimethylarginine, N^ϵ-Mono-, Di-, and Trimethyllysine, and Glucosylgalactosyl- and Galactosyl-δ-hydroxylysine from Human Urine

(Received for publication, May 18, 1970)

Yasuo Kakimoto and Shigenori Akazawa

From The Department of Neurology, The Institute of Higher Nervous Activity, Osaka University Medical School, Fukushima-ku, Osaka, Japan

"ADMA and SDMA may be important for the study of various pathological states"

Protein

PRMT

Protein with ADMA residues

hydrolysis

ADMA

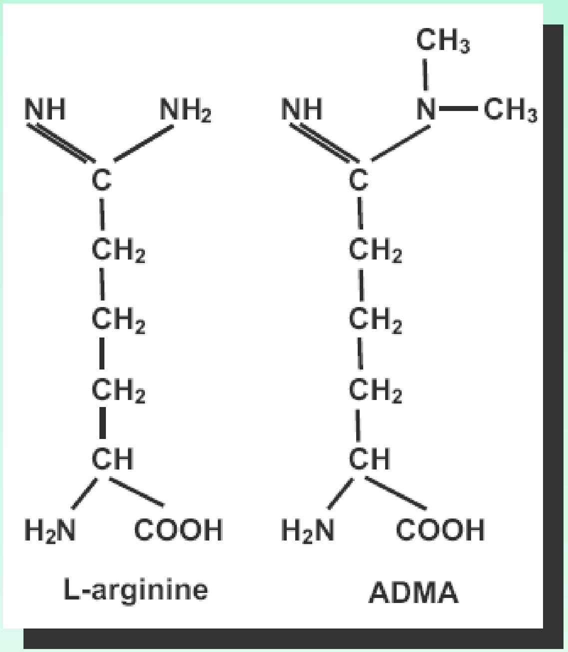
inhibition

L-arginine

NOS

NO

+ citrulline



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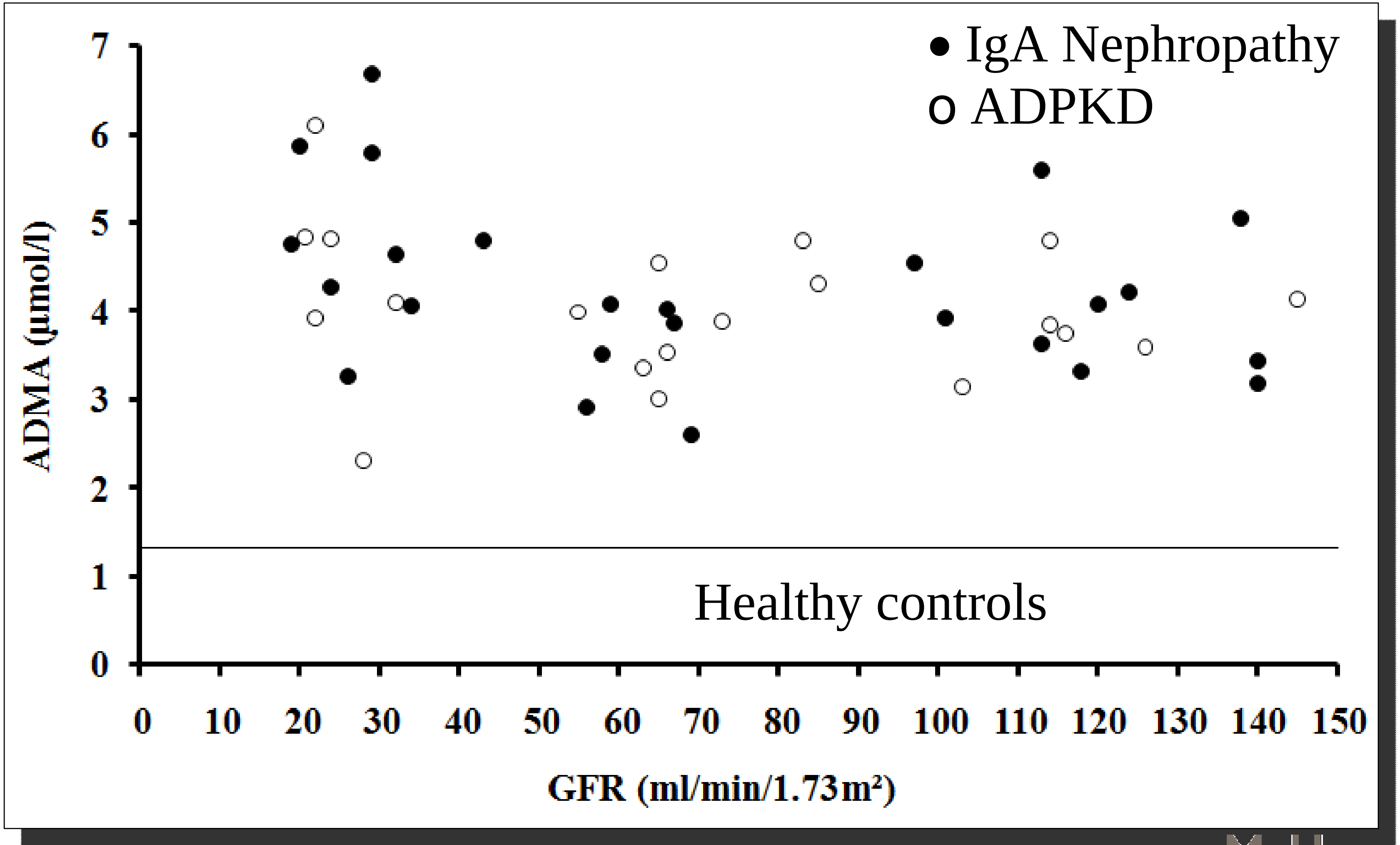
Marked increase of asymmetric dimethylarginine in patients with incipient primary chronic renal disease

KIELSTEIN et al. ***J Am Soc Nephrol*** **13: 170-176, 2002**



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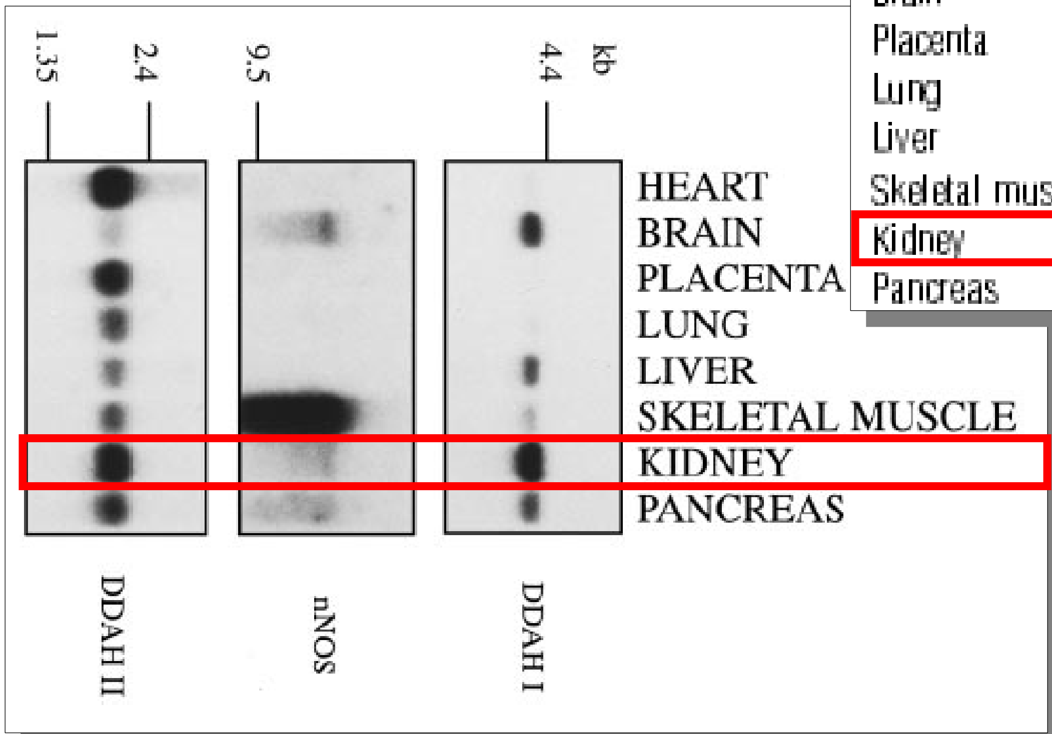
Identification of two human dimethylarginine dimethylaminohydrolases with distinct tissue distributions and homology with microbial arginine deiminases

LEIPER et al. *Biochem J* 343:209-214, 1999

Tissue	Content of isoform (% of maximum)	
	DDAH I	DDAH II
Heart	15	100
Brain	56	19
Placenta	12	56
Lung	16	36
Liver	42	26
Skeletal muscle	27	25
Kidney	100	70
Pancreas	47	34



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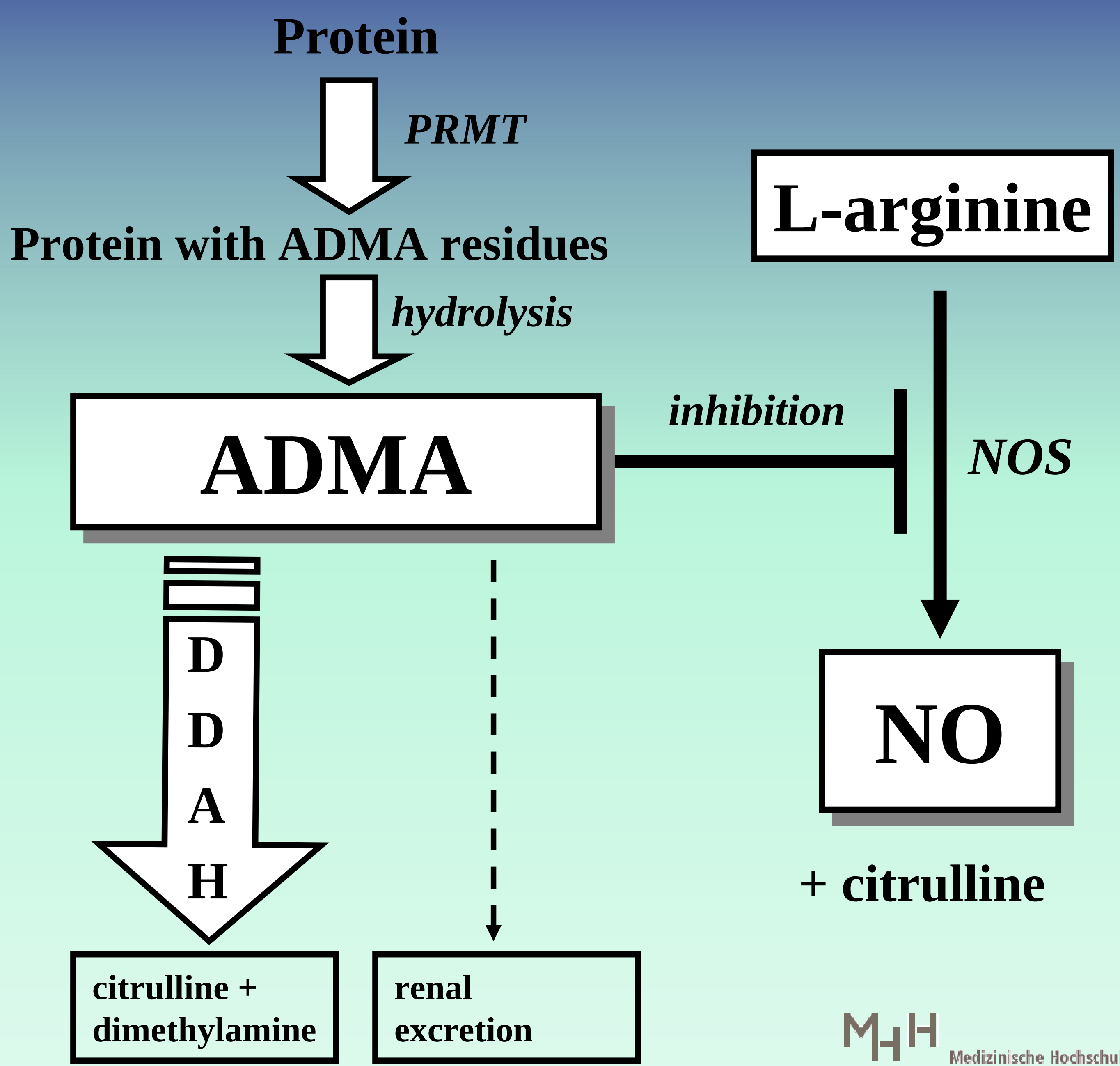

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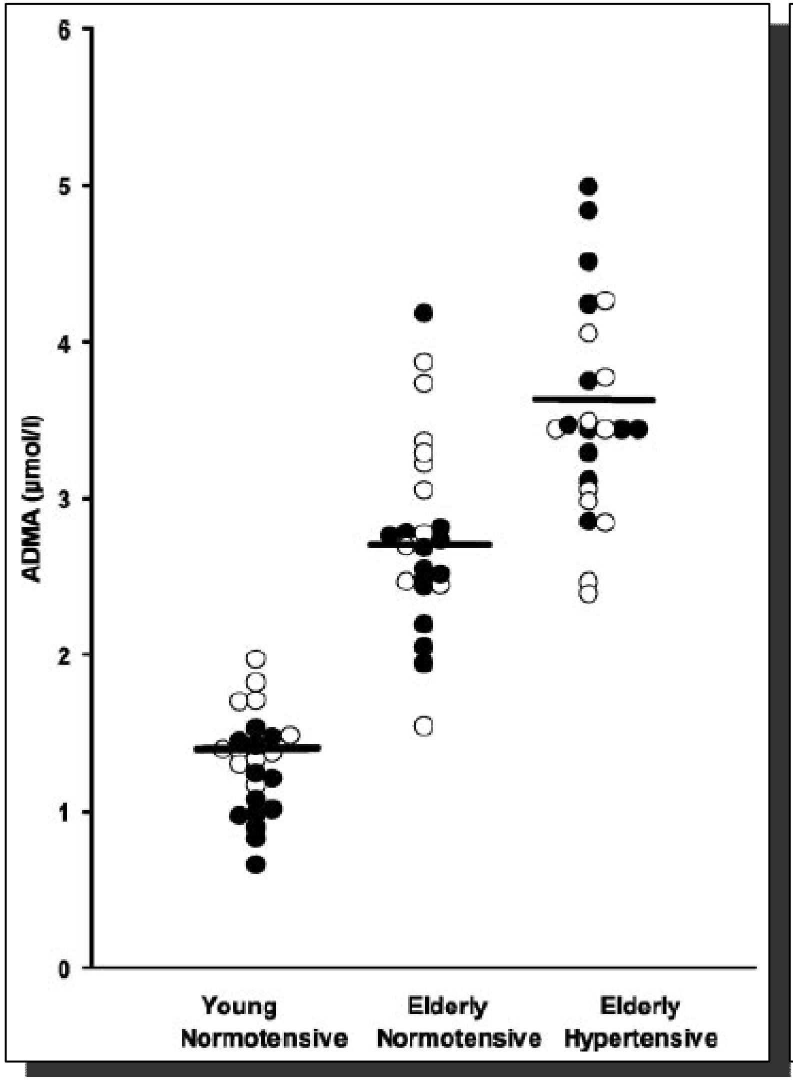
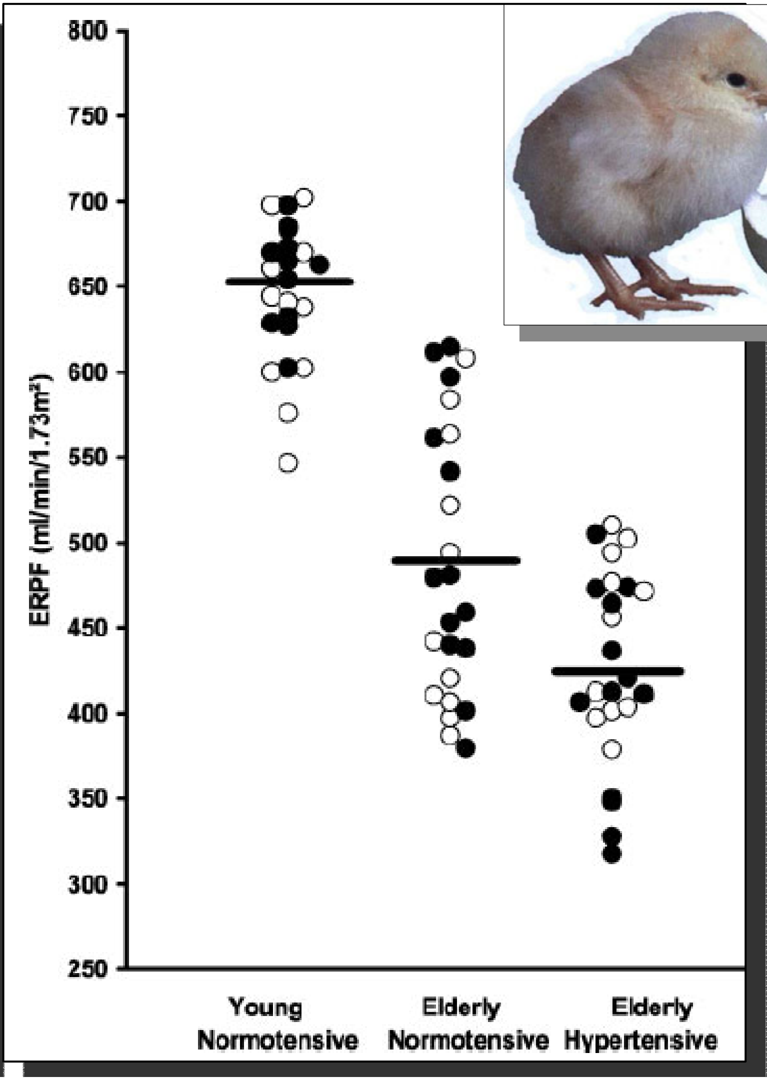
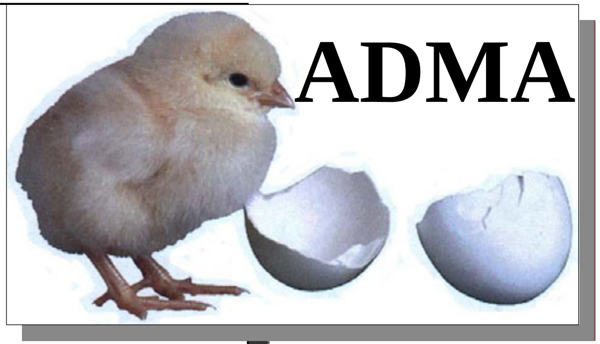
Asymmetric dimethylarginine (ADMA), blood pressure and renal perfusion in elderly subjects.

KIELSTEIN et al. *Circulation* 107:1891-1895, 2003







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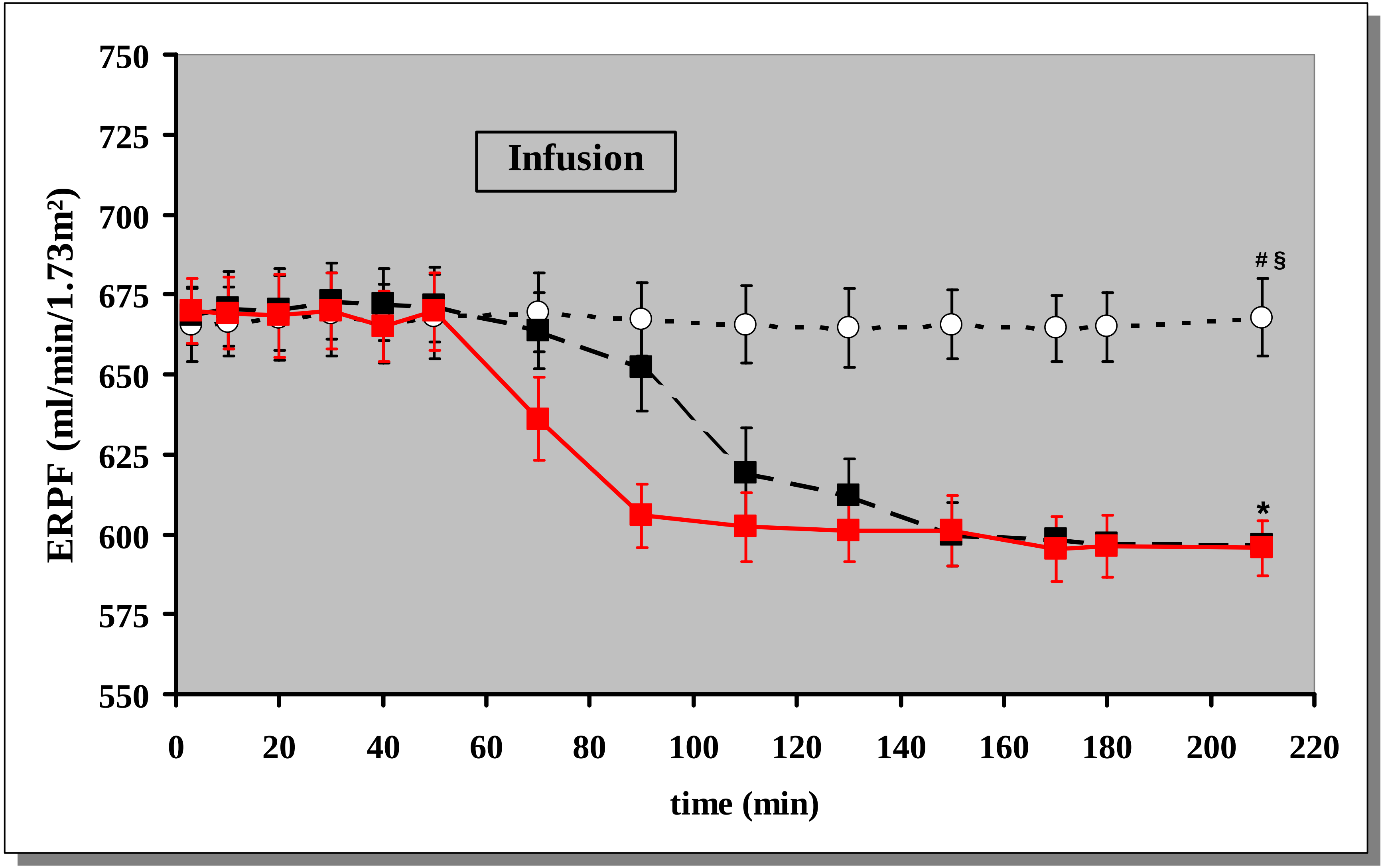
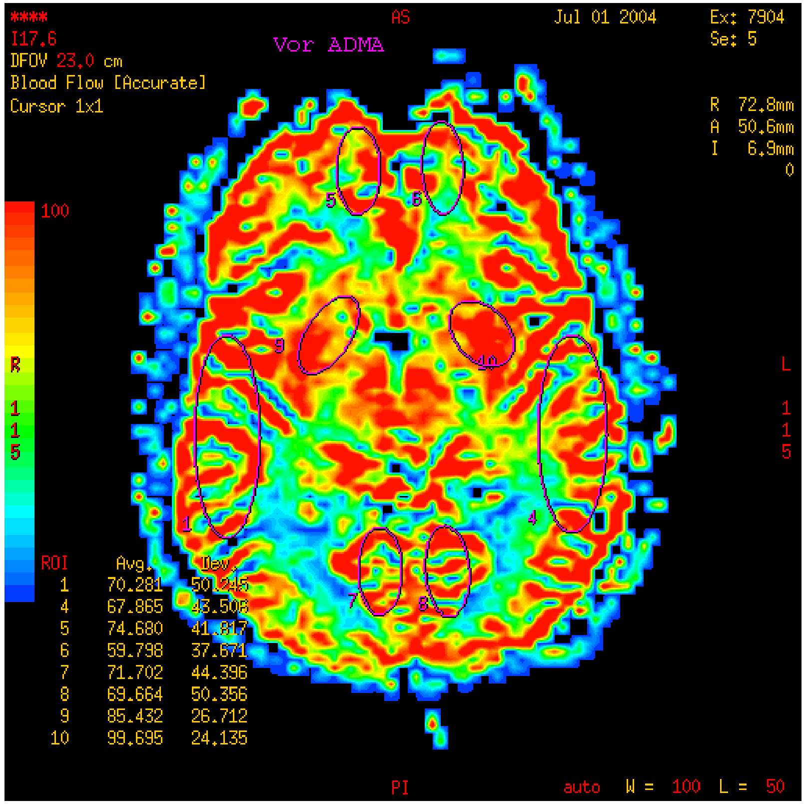
Cardiovascular effects of systemic nitric oxide synthase inhibition with asymmetrical dimethylarginine in humans

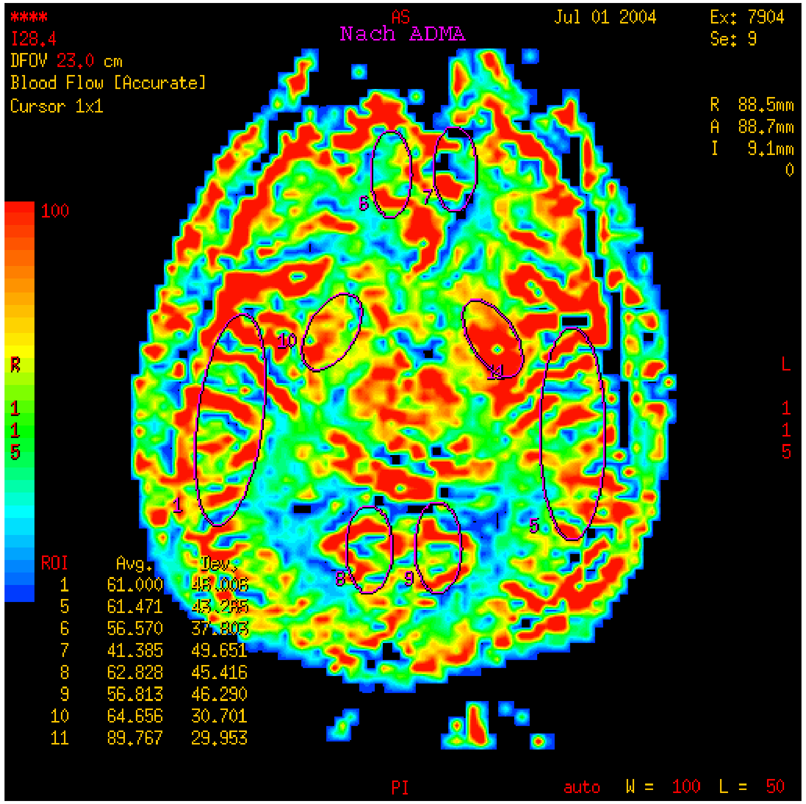
KIELSTEIN et al. *Circulation* 109: 172-177, 2004



ADMA increases arterial stiffness and decreases cerebral blood flow in human

KIELSTEIN et al. *Stroke* 37:2024-9, 2006





before ADMA **after ADMA**

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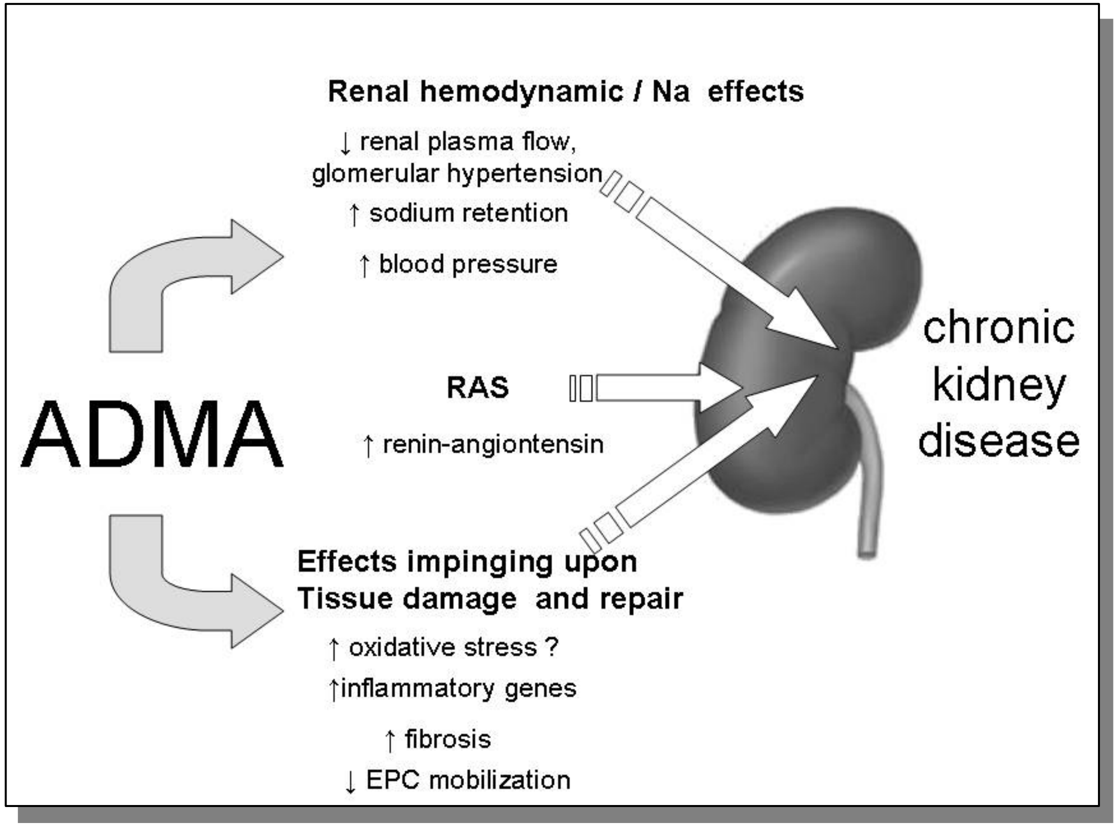
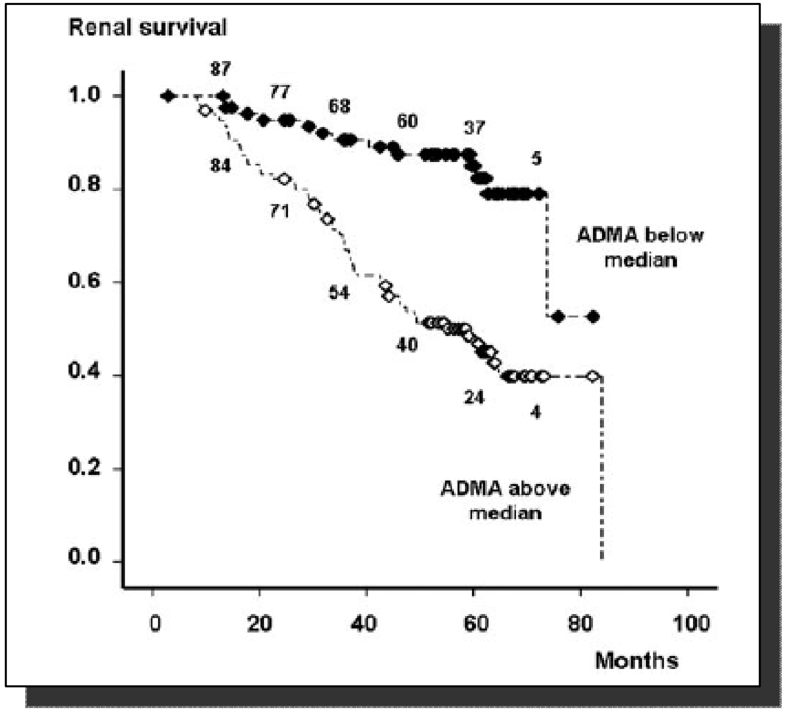
Asymmetric dimethylarginine: a novel marker of risk and a potential target for therapy in chronic kidney disease.

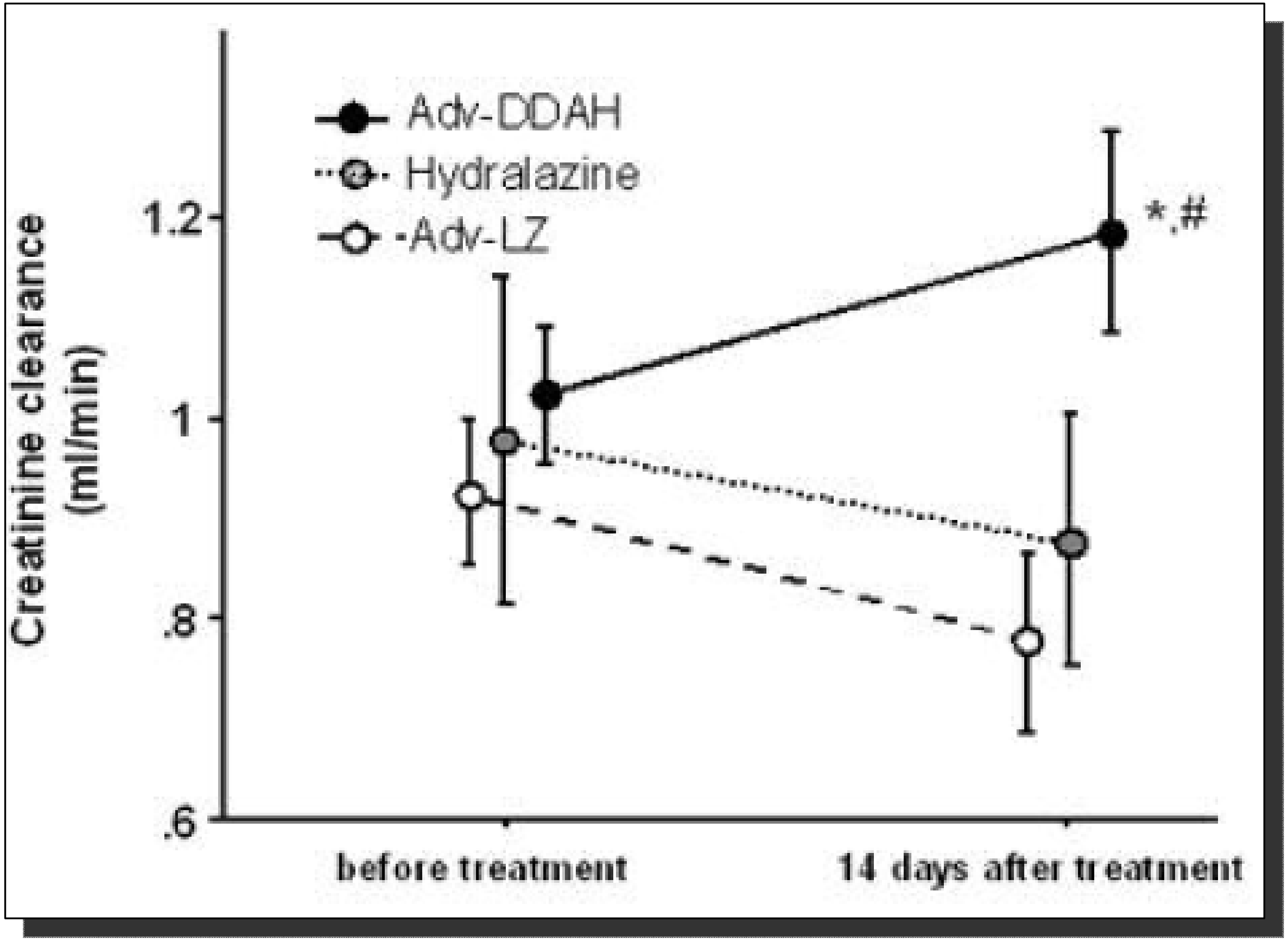
ZOCCALI & KIELSTEIN ***Curr Opin Nephrol Hypertens*** **15:314-320, 2006**





DDAH prevents progression of renal dysfunction by inhibiting loss of peritubular capillaries and tubulointerstitial fibrosis in a rat model of CKD

MATSUMOTO et al. JASN 18: 1525–1533, 2007



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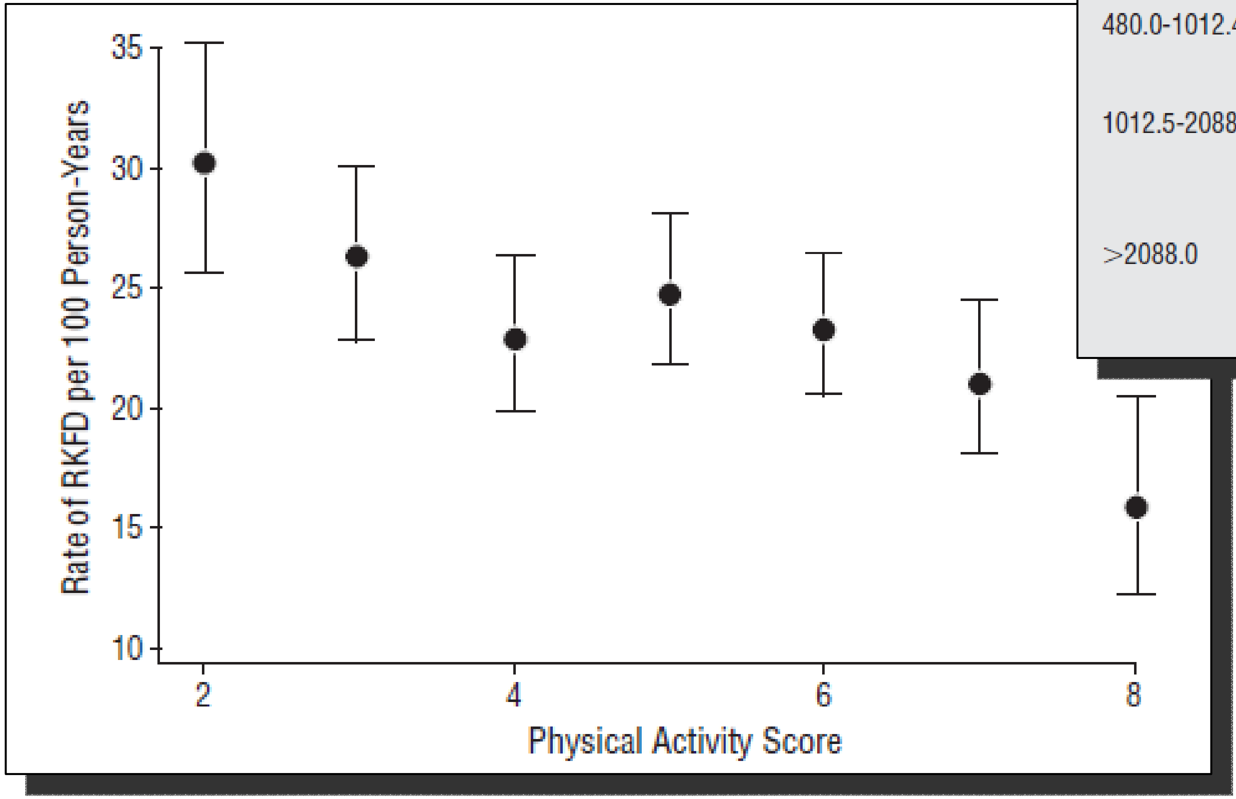
Physical Activity and Rapid Decline in Kidney Function Among Older Adults

ROBINSON-COHEN et al. *Arch Intern Med* 169:2116-2123, 2009

Kilocalories of Leisure-Time Activity per Week, No.	Example Activities
<105.0	Walking 20 min/wk, bowling 30 min/wk, or performing low-impact aerobics 15 min/wk
105.0-479.9	Walking 10 min/d, bowling 2 h/wk, or performing low-impact aerobics 30 min/wk
480.0-1012.4	Walking 20 min/d, playing golf using a cart 4 h/wk, or swimming laps 60 min/wk
1012.5-2088.0	Walking 40 min/d, playing golf walking and pulling clubs 4 h/wk, or playing tennis, singles or doubles, 2 h/wk
>2088.0	Walking 90 min/d, playing golf walking and pulling clubs 8 h/wk, or swimming laps 3 h/wk



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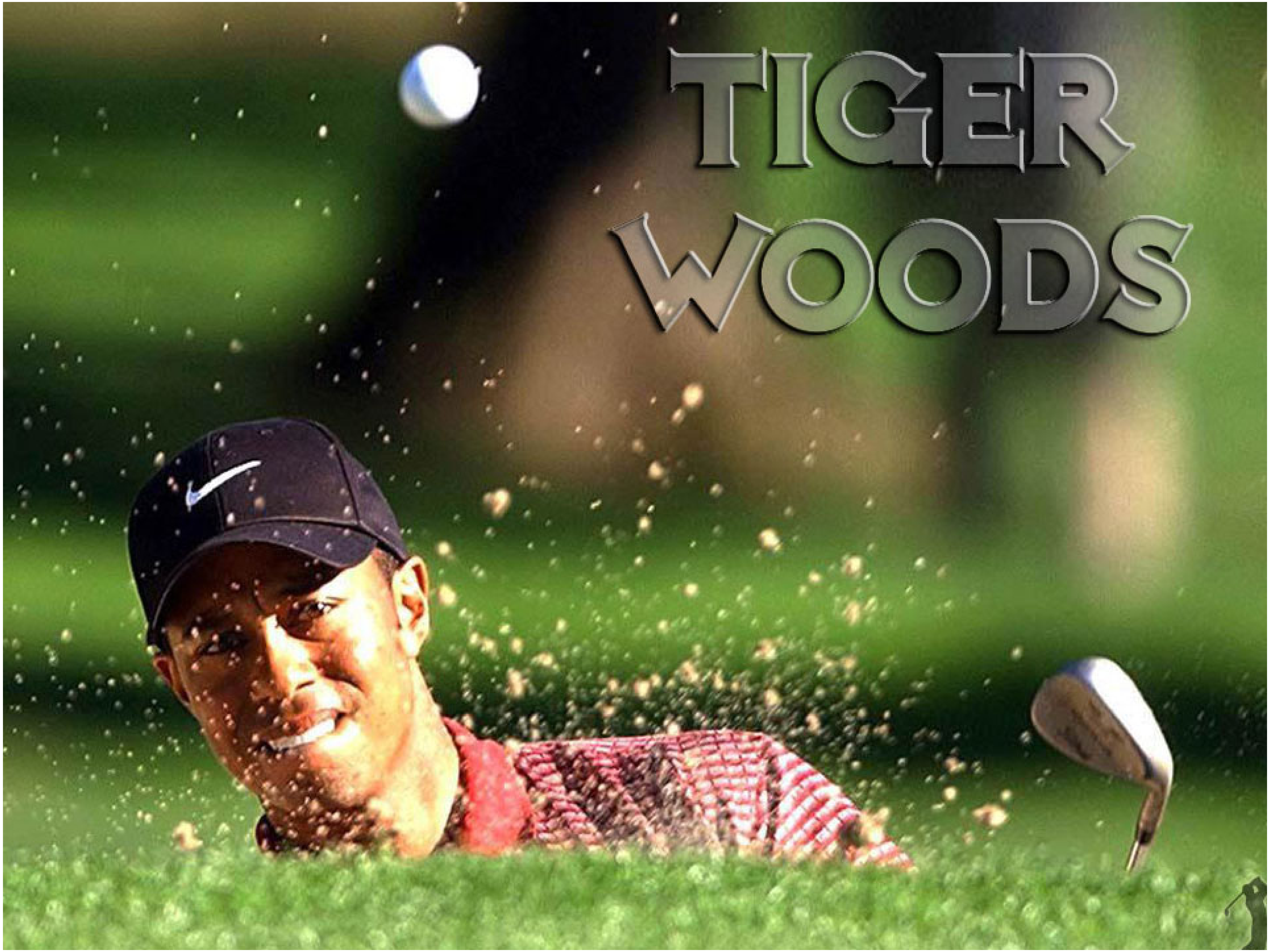
TIGER
WOODS


BONS BAISERS
DE RUSSIE
(FROM RUSSIA WITH LOVE)