Estimating GFR in Children: Taking the PEE out of the Equation

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for the CKiD Study Group

Chronic Kidney Disease in Children

Table 1. Stages of Chronic Kidney Disease (CKD), Prevalence in the United States in 2000, and Stage-Specific Recommendations for Detection, Evaluation, and Management.

Stage of CKD	Description	GFR	Detection, Evaluation, and Management*	Prevalence†	
				%	No. of Cases (95% CI)
		ml/min/1.73 m²			*millions*
1	Kidney damage with normal or increased GFR	>90	Diagnosis and treatment Treatment of coexisting conditions Slowing progression Risk reduction for cardiovascular disease	2.8	5.6 (4.0–7.2)
2	Kidney damage with mild decrease in GFR	60–89	Estimation of progression	2.8	5.7 (4.2–7.2)
3	Moderate decrease in GFR	30–59	Evaluation and treatment of complications	3.7	7.4 (6.0–8.9)
4	Severe decrease in GFR	15–29	Referral to nephrologist and consideration for kidney replacement therapy	0.1	0.30 (0.02–0.5)
5	Kidney failure	<15	Replacement (if uremia present)	0.2	0.30‡

19 million adults with early stages of Chronic Kidney Disease (GFR < 60 ml/min/1.73m^2 or presence of kidney damage (proteinuria) x > 3 mo. By 2030 > 2 million people will need dialysis or kidney transplantation for kidney failure.

Stevens NEJM 354:2473, 2006

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Estimation of GFR
Endogenous Substances

- **Creatinine: secreted, affected by diet, muscle mass, chronic illness; extrarenal elimination of Cr from gut.**
- **Cystatin: cleared by kidneys, cannot measure clearance, influenced by steroids, age, sex, wt, ht, smoking status, CRP, extrarenal elimination**

Table 2. **Factors Affecting Creatinine Generation.***

Factor	Effect on Serum Creatinine
Aging	Decreased
Female sex	Decreased
Race or ethnic group†	
Black	Increased
Hispanic	Decreased
Asian	Decreased
Body habitus	
Muscular	Increased
Amputation	Decreased
Obesity	No change
Chronic illness	
Malnutrition, inflammation, deconditioning (e.g., cancer, severe cardiovascular disease, hospitalized patients)	Decreased
Neuromuscular diseases	Decreased
Diet	
Vegetarian diet	Decreased
Ingestion of cooked meat	Increased

* Variation in muscle mass accounts for the predominant proportion of creatinine generation.
† White race served as the reference group.

Recommend more accurate determination of GFR in pts with unusual body habitus or diet, rapidly changing kidney function, GFR > 60 as for kidney donation.

Stevens NEJM 354:2473, 2006

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Prediction Equations to Determine Glomerular Filtration Rate (GFR) in Adults

- **MDRD formula:**

  GFR = 186 x [Creatinine (μmol/l) x 88.4] $^{-1.154}$ x [age] $^{-0.203}$ x [0.742 if female] x [1.212 if black]

- **Cockcroft-Gault formula:**

  GFR = (140 – age) x weight (kg) x (1.23 if male, or 1.05 if female) x 1.73/BSA (m^2) / Creatinine (μmol/l)

- **Cystatin C formula:**

  GFR = (80.35/cystatin C concentration (mg/ml)) – 4.32

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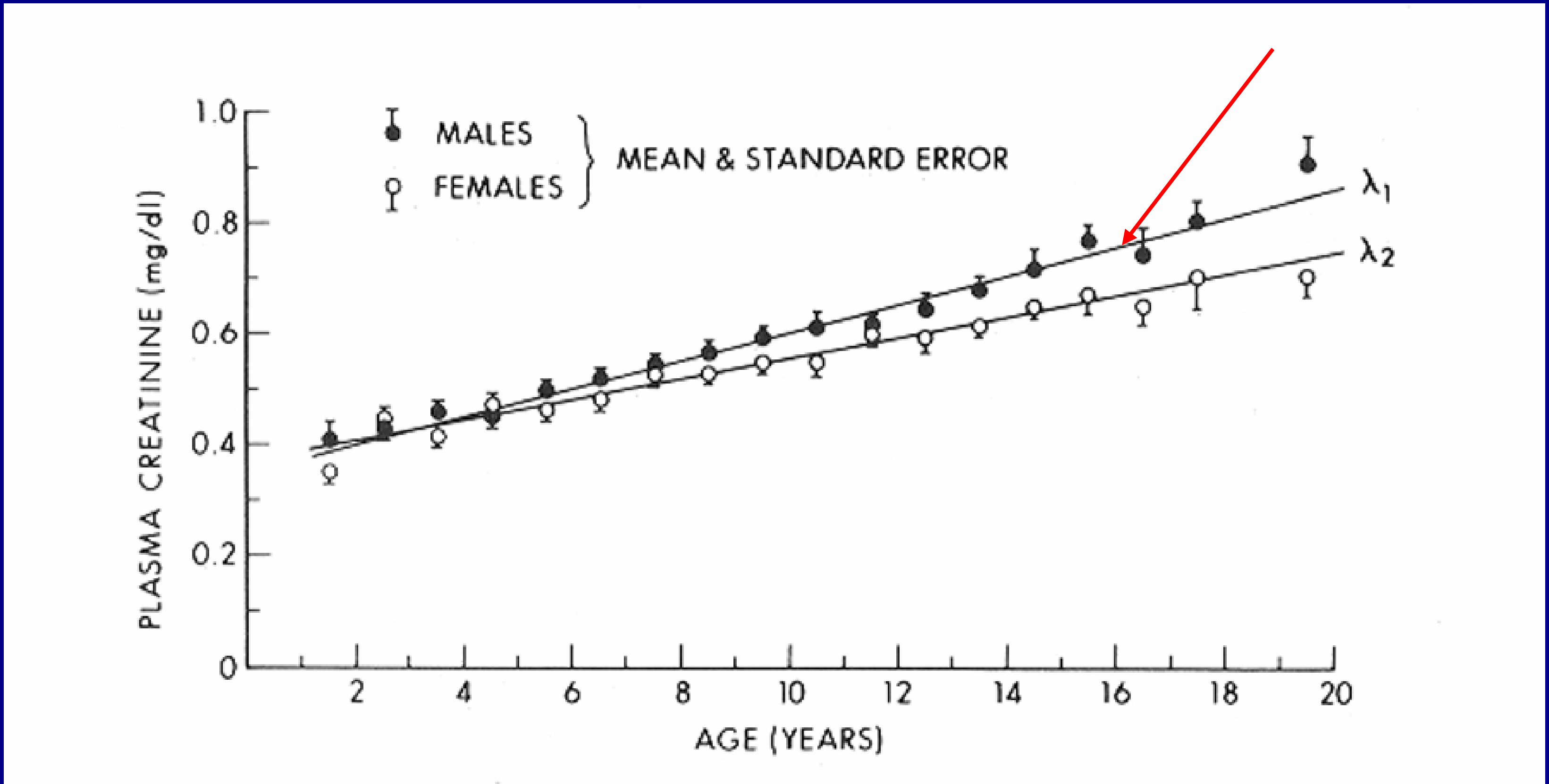
Pcr as a Function of Age: Yearly Mean Data in Normals



*Males have significantly higher Pcr in late adolescence

Schwartz et al, J Pediatr 88:828, 1976

Derivation of k

- **Ccr (ml/min/1.73 m^2) = UcrV/Pcr * 1.73/SA**
- **Assumptions:**
  - SA proportional to L^2
  - UcrV = creatinine production rate
  - Creatinine production rate proportional to muscle mass
  - Muscle mass proportional to L^3
  - So, UcrV proportional to L^3 and:
- **Ccr = k'* (L^3/Pcr) * (1.73/L^2) = k * L/Pcr**
  - k = 1.73 * k' (mg creatinine per 100 min * cm * 1.73 m^2)

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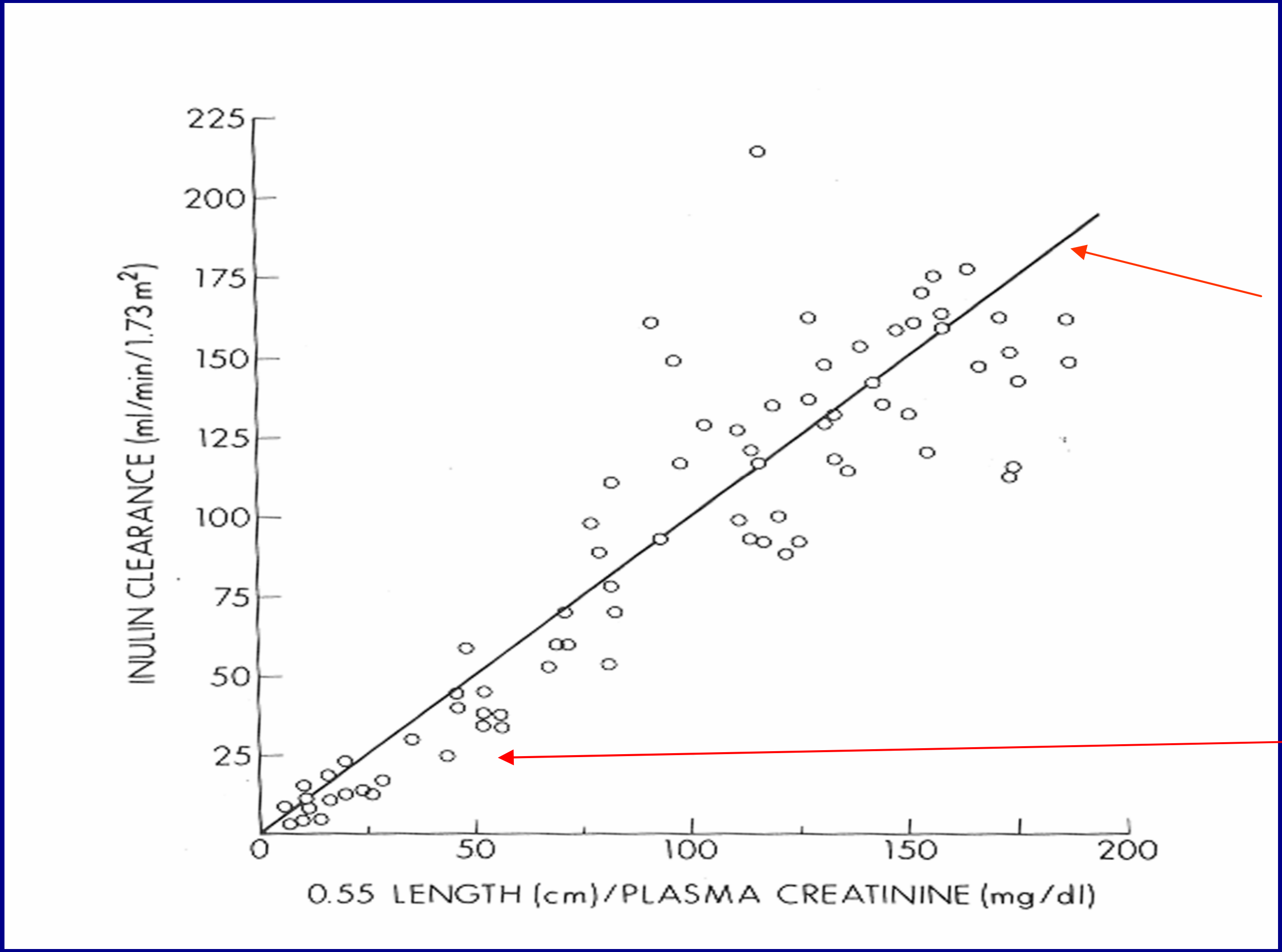
Cin vs. 0.55*L/Pcr



Line of identity

Overestimates Cin

Schwartz et al, Pediatrics 58:259, 1976

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Values of k in Pediatrics
(Modified Jaffe method)
eGFR=k Ht/Scr

- Premature infants: k=0.33
- Term infants: k=0.45
- Children, teen females: k=0.55
- Males $\geq$ 13 y: k=0.7

Schwartz Ped Clin N Amer 34:571, 1987

Markers for GFR

Table 1 Pharmacokinetic properties of markers of glomerular filtration

	Inulin	Creatinine	Iothalamate	DTPA	EDTA	Iohexol
Molecular weight (Da)	5200	113	614	393	292	821
Elimination half-life (min)	70	200	120	110	120	90
Plasma protein binding (%)	0	0	< 5	5	0	< 2
Volume of distribution	ECS	Total body water	ECS	ECS	ECS	ECS

ECS, extracellular space; DTPA, diethylenethiaminepenta-acetic acid; EDTA, ethylenediaminetetra-acetic acid.

Inulin ~ polyfructosan
^{125}I-Iothalamate = Glofil
Iohexol = Omnipaque contrast media

Rahn et al, J Hypertension 17:309, 1999

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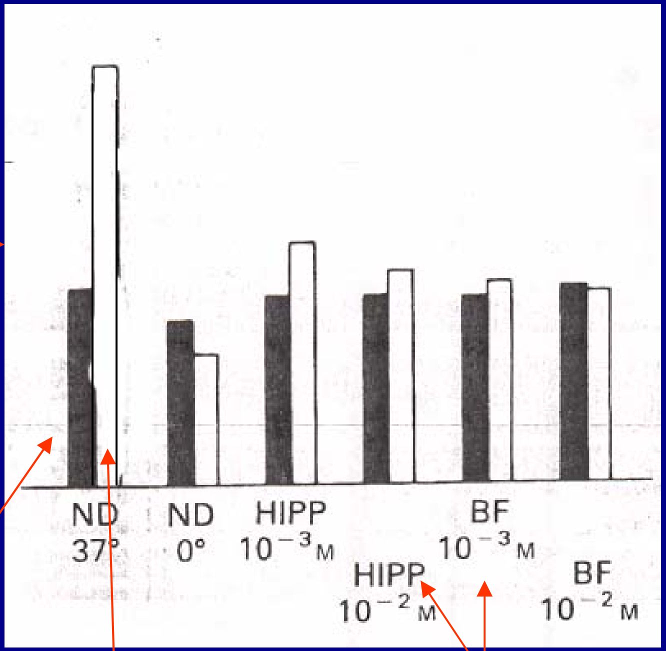
Iothalamate is Secreted by the Kidney

- Odlind et al, KI 27:9, 1985 conclude that iothalamate is not an ideal marker for GFR
- Renal cortical slice tissue-to-medium (T/M) ratios of ^{125}I iothalamate were twice those of ^{51}Cr-EDTA and were reduced by organic anion transport inhibitors
- Simultaneous ^{51}Cr-EDTA and ^{125}I iothalamate plasma clearances in 11 studies
  - In each one C-Ioth > C-EDTA, ave. 13% higher, P<0.001, and this was reduced by probenecid to 7%



Iohexol

- **Non-ionic contrast agent (Omnipaque[R])**
- **MW 821**
- **No protein binding**
- **No side effects (one felt a transient hot flush)**
  - No contrast nephropathy
  - Does not affect C_{EDTA} => does not alter GFR
- **Stable in serum & urine at room Temp x 24 h**
  - Unaffected by freezing & thawing
- **100% of iohexol is recovered unmetabolized in urine after 12 h**
  - Renal Ciohexol = Total (plasma) Ciohexol
- **Total CV = 11.4% (methodologic = 5.3%, biologic ~ 10%)**
- **Apparent V_D = 0.27 L/kg => extracellular water**

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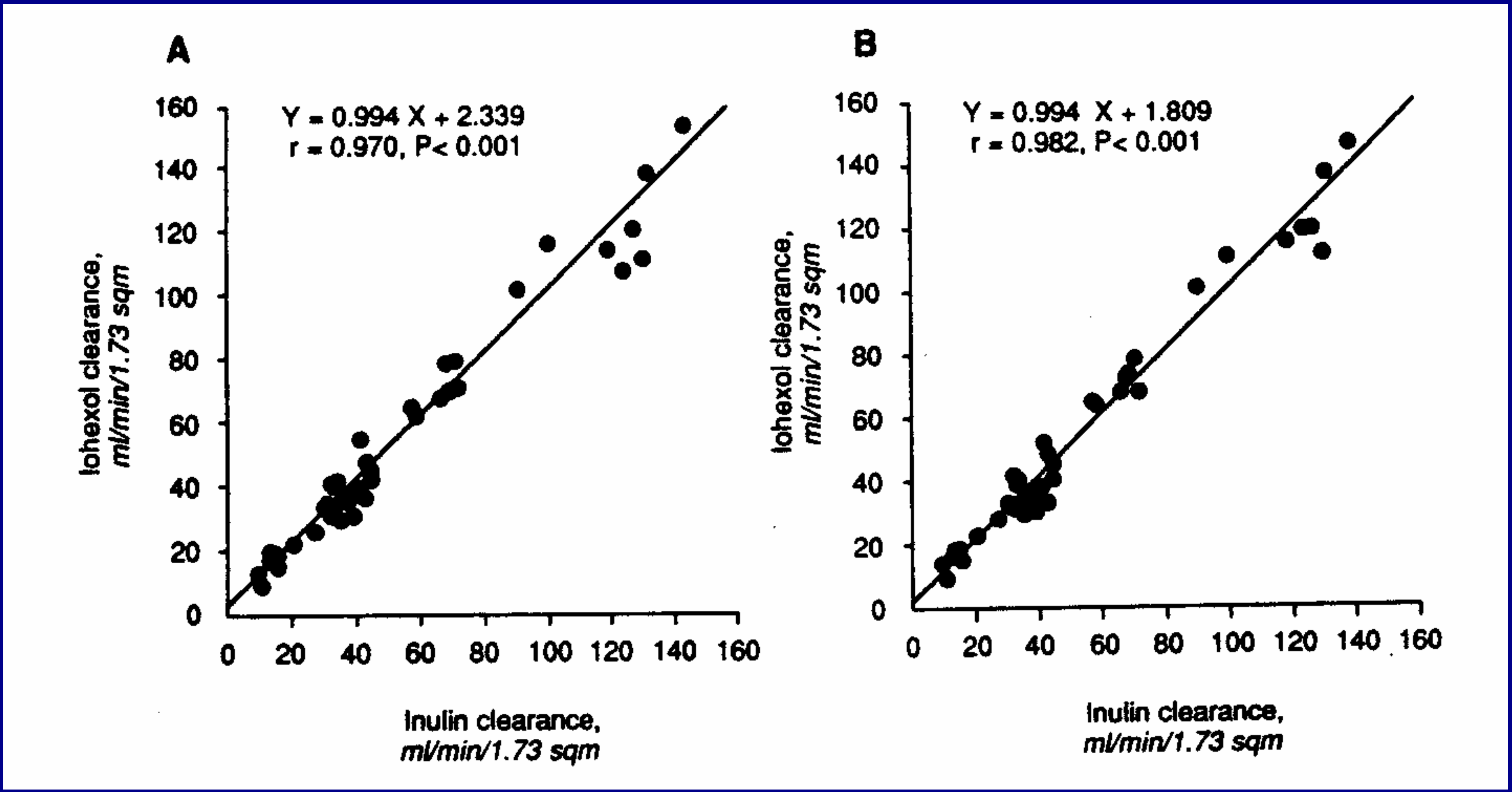
Excellent correlation between renal Cin and plasma Ciohexol



2 compartment model

1 compartment model (Brochner-Mortensen)

Gaspari, JASN 6:257, 1995

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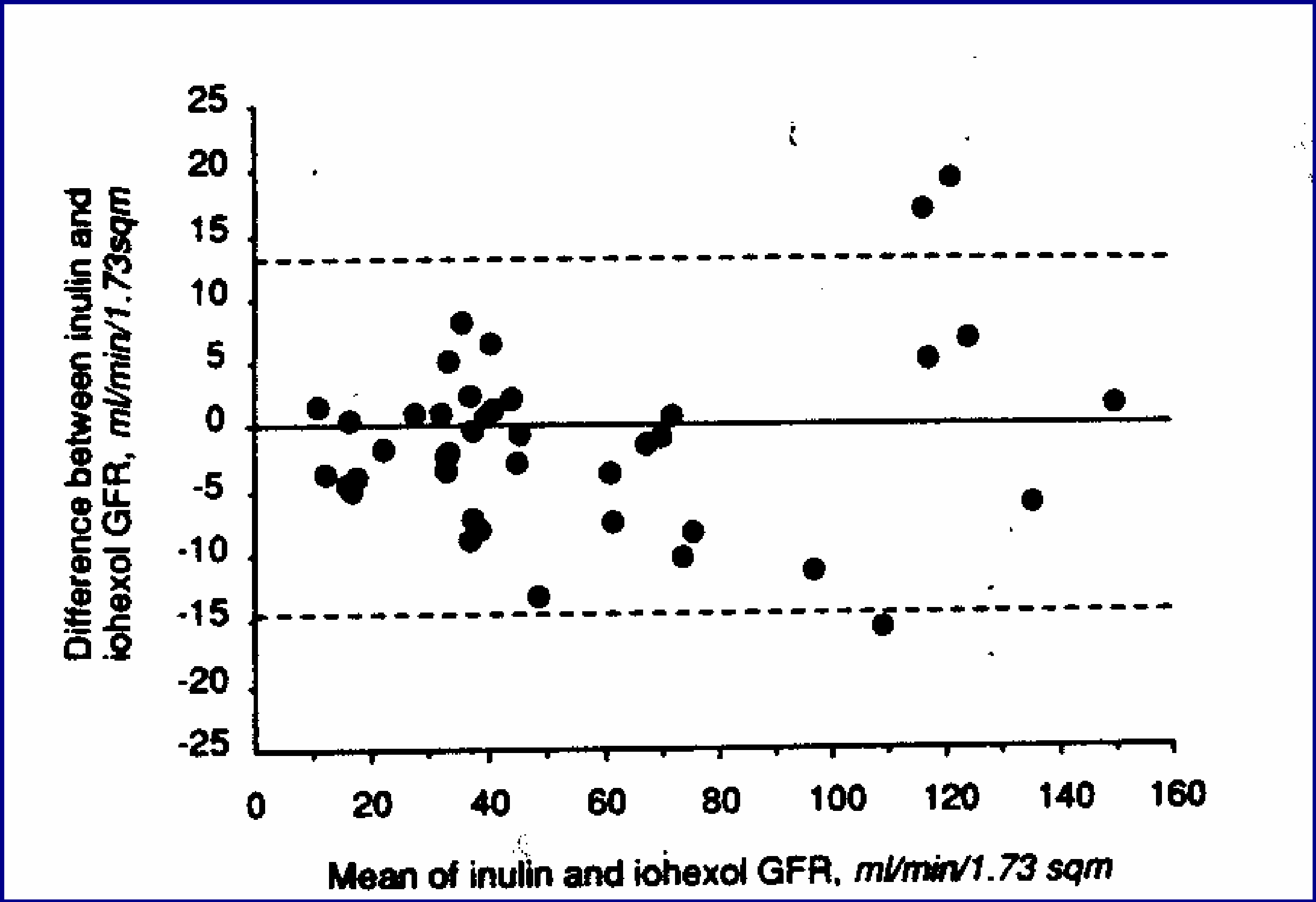

Bland-Altman showing differences between plasma iohexol and renal inulin clearances.

Gaspari, JASN 6:257, 1995

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Pilot Study
To Assess Iohexol GFR

- **Children w/ reduced GFR (GCHAS, Johns Hopkins)**
  - Normal bladder emptying; no VUR
- **Water load 5-10 cc/kg, replace urine cc/cc x 3-4 collections**
- **Blood & urine for Creat & Iohexol**
- **Iohexol (5 cc) iv, plasma disappearance**
  - Samples (100 ul) @ 5, 10, 20, 30, 60, 120, 180, 240, 300, & 360 min (5 min point not accurate)
  - Use 9 and 4 point determinations for 2 compartments
    - 10, 30, 120, 300 min
  - Also 1-compartment BM model – 120 and 300 min
  - Determines # and time of samples for NIH CKiD study

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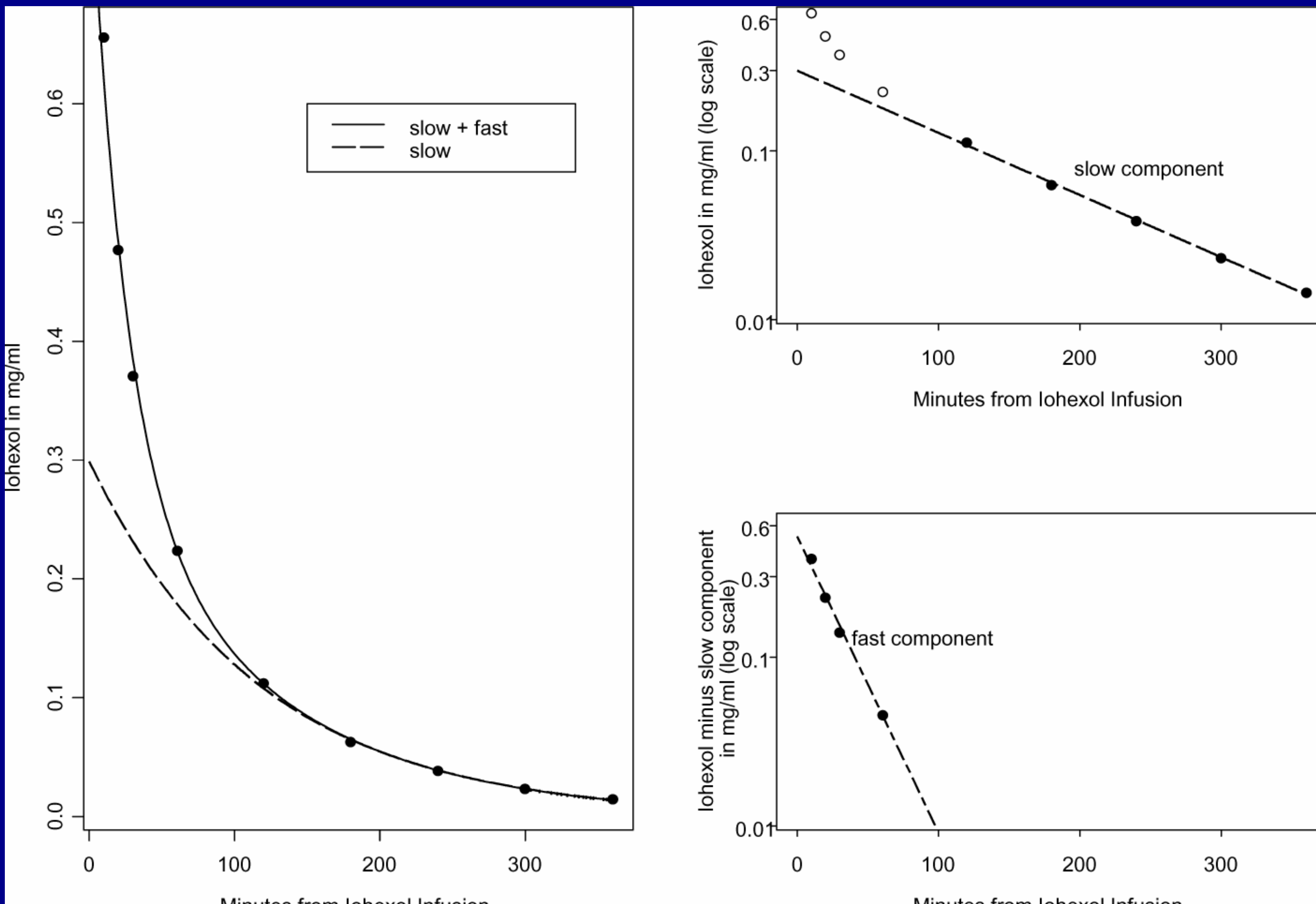
Iohexol Disappearance from Blood

Kidney Int 69:2070, 2006



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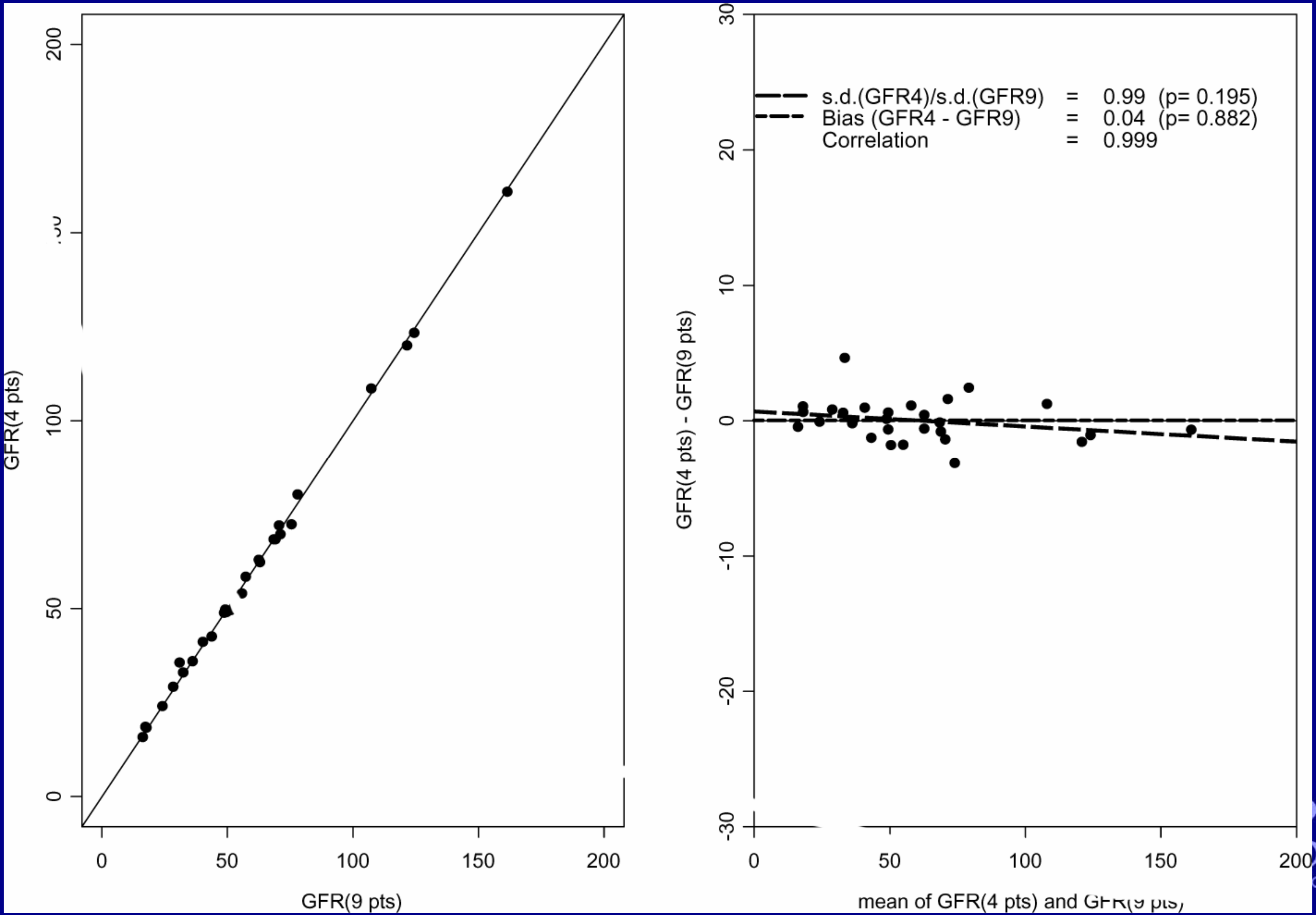
Two Compartment Models:
GFR4 agrees with GFR9
Kidney Int 69:2070, 2006



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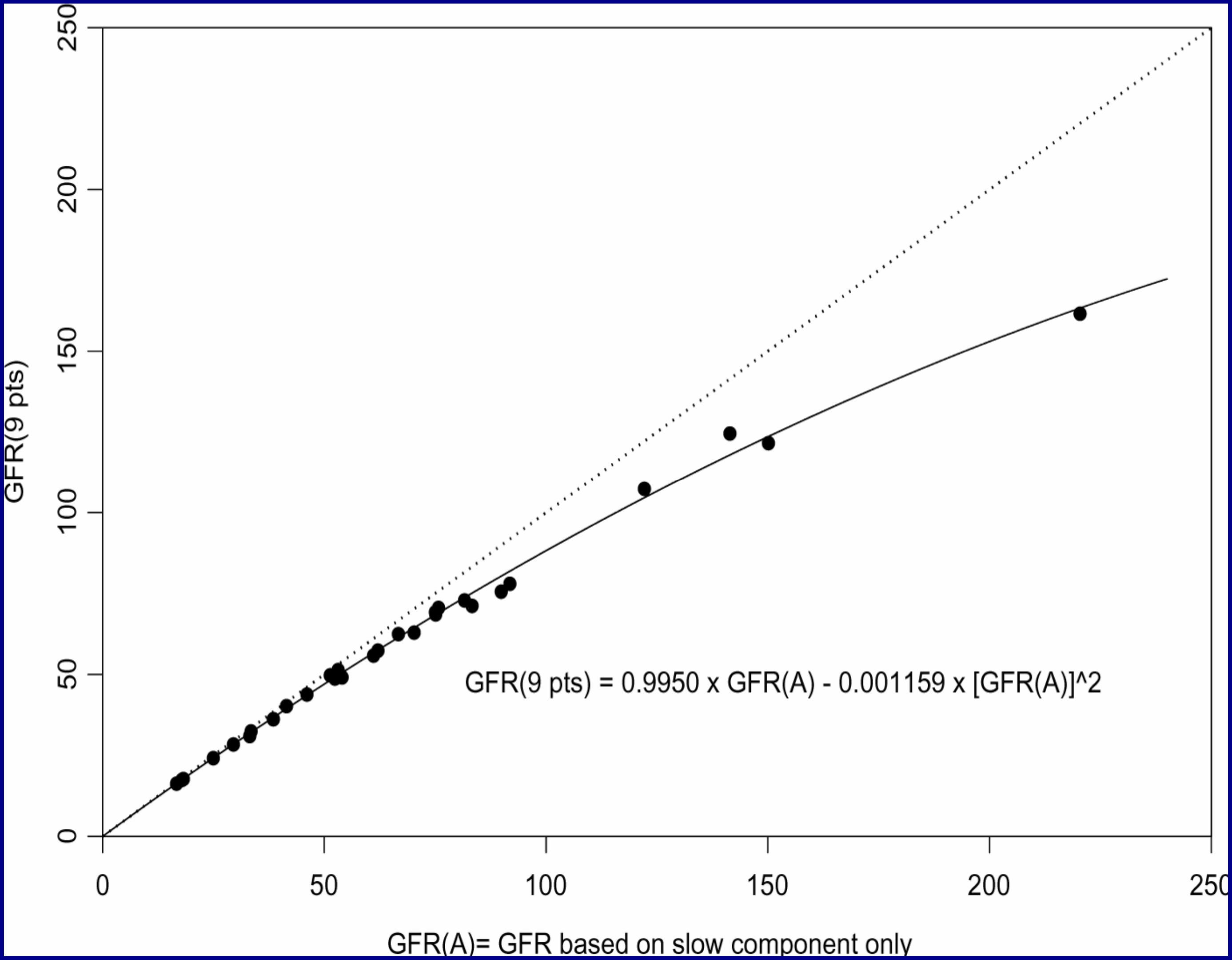
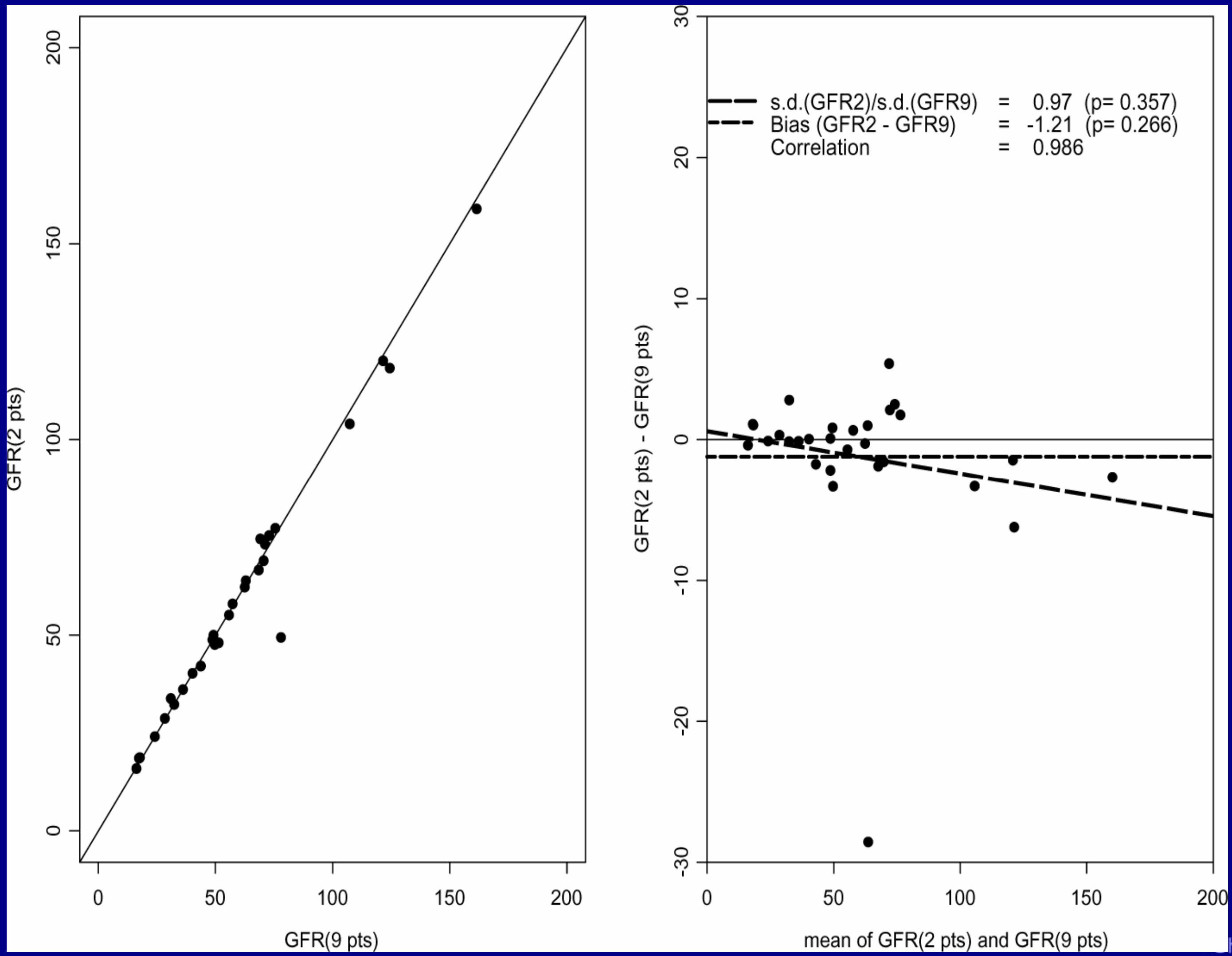
One Compartment model: *Overestimates* GFR but *Fits* BM kinetics

Kidney Int 69:2070, 2006



GFR2 ~ GFR9

Kidney Int 69:2070, 2006



Brochner-Mortensen Coefficients

Kidney Int 69:2070, 2006 & CKiD Data

Method	C1 [GFR(2)]	C2[GFR(2)]^2
BM Adults (**^{51}Cr-EDTA**)	**0.99078**	**-0.001218**
BM Children (**^{51}Cr-EDTA**)	**1.01**	**-0.0017**
Pilot (**iohexol**) **CKiD** (**iohexol**)	**0.9950** **1.0112**	**-0.001159** **-0.001447**

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CKiD Iohexol Protocol

- At Sites of the CCCs (S Furth, B Warady):
  - Infusion: 5ml ~3200 mg of Iohexol i.v.
  - Blood samples taken at 10, 30, 120 and 300 minutes after infusion for GFR4.
- Central Blood Laboratory (G Schwartz) measures concentrations and enters them into database.
- CCCs enter data.
- KIDMAC (S Su, J Xu, J Jerry, A Muñoz, C Pierce, A Wentz) implements algorithm to calculate GFR and weekly updates database for web-based reports.

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CANADA
Edmonton
Vancouver
Regina
Winnipeg
Québec
Ottawa
Montréal
Toronto
Seattle
Olympia
Washington
Salem
Oregon
Idaho
Boise
Montana
Helena
North Dakota
Bismarck
Minnesota
Saint Paul
South Dakota
Pierre
Wyoming
Cheyenne
Wisconsin
Madison
Michigan
Lansing
Detroit
Maine
Augusta
Montpelier
Vt.
N.H.
Concord
Boston
Mass.
Albany
New York
Providence
R.I.
Hartford
Conn.
New York
Pennsylvania
Trenton
Philadelphia
New Jersey
Harrisburg
Dover
Del.
Md.
Annapolis
Washington, D.C.
Richmond
Virginia
West Virginia
Charleston
Ohio
Columbus
Indiana
Indianapolis
Illinois
Springfield
Chicago
Iowa
Des Moines
Nebraska
Lincoln
Sacramento
Carson City
Nevada
Salt Lake City
Utah
San Francisco
California
Las Vegas
Los Angeles
Colorado
Denver
Kansas
Topeka
St. Louis
Jefferson City
Missouri
Kentucky
Frankfort
Raleigh
North Carolina
Nashville
Tennessee
Memphis
Oklahoma
Oklahoma City
Arkansas
Little Rock
Arizona
Phoenix
New Mexico
Santa Fe
Columbia
South Carolina
Atlanta
Georgia
Alabama
Montgomery
Mississippi
Jackson
Louisiana
Baton Rouge
New Orleans
Dallas
Texas
Austin
Houston
Tallahassee
Florida
Miami
Mexicali
Hermosillo
Chihuahua
Monterrey
MEXICO
North Pacific Ocean
North Atlantic Ocean
Gulf of Mexico
THE BAHAMAS
Nassau
State capital
Scale 1:27,000,000
Albers Equal-Area Projection
Standard parallels 28°30'N and 45°30'N
500 Kilometers
500 Miles
River

in Children

CKiD Study Goals

- Recruit & retain 540 children, aged 1-16 yrs, eGFR 30 – 90 ml/min/1.73m^2 in a longitudinal cohort study
- Define risk factors for CKD progression
- Define effects of CKD progression on:
  - Neurocognitive development/function
  - Prevalence of CVD risk factors
  - Growth failure

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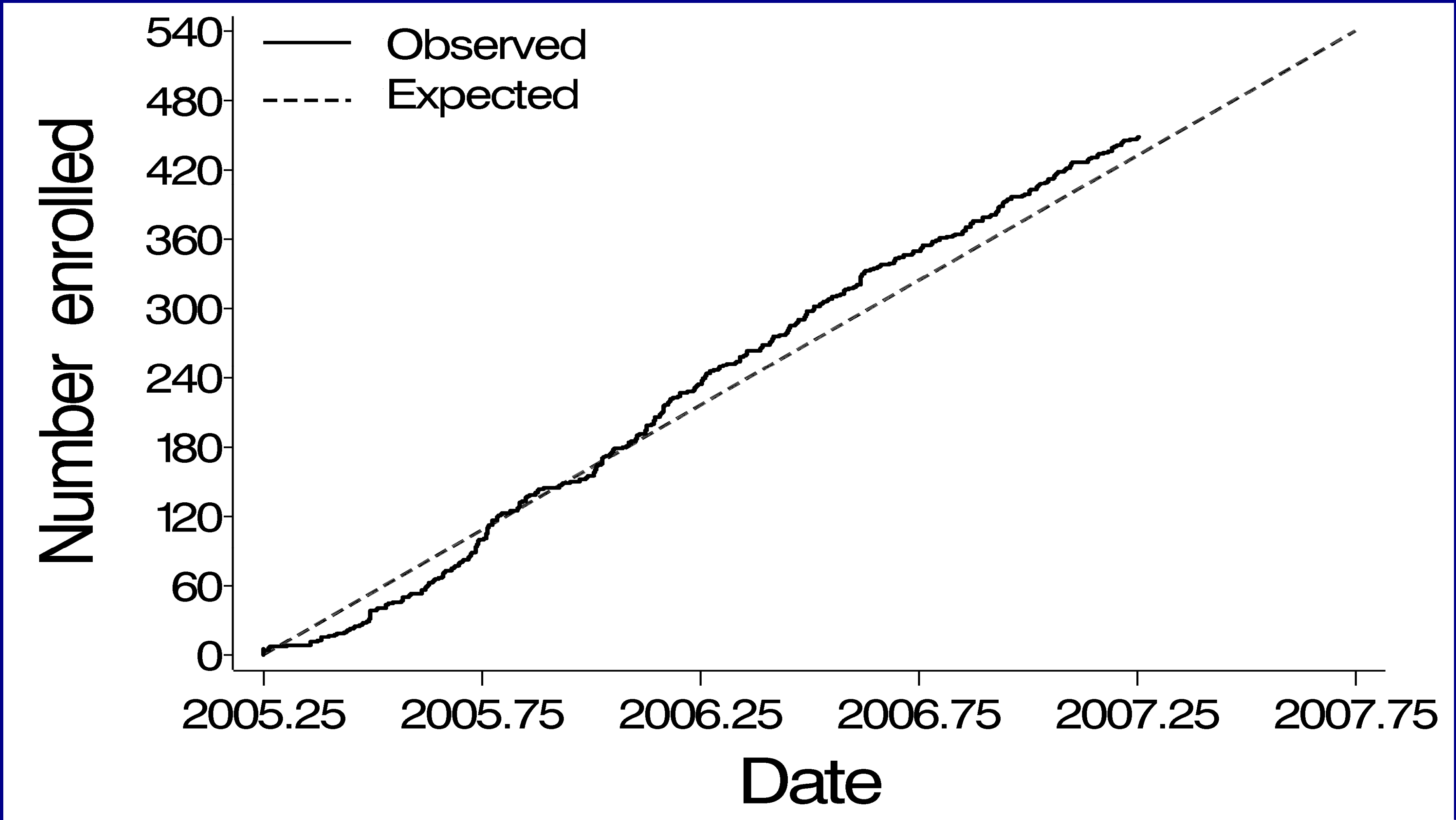
Patient Recruitment



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Measurements According to Time-on-Study

Enrollment

Measurements	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Kidney:, Renal Panel*, CBC* **CV:** Standardized BP* **Neurocognitive:** Peds QL* **Growth:** Height*, Weight*, Tanner Stage*	√	√	√	√	√	√
GFR (Iohexol) Cystatin C	√	√		√		√
Echo, ABPM, Carotid IMT		√		√		√
Cognitive, Behavior Testing	√		√		√	
wrCRP, Lipids	√		√		√	

*Locally performed tests

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Demographics

Variable	Median or %	5th %ile	95th %ile
CKD Cause			
Glomerulonephritis	21%		
Non-GN (Urologic/Cystic Hereditary)	67%		
Non-GN (Other)	6%		
Missing/Unknown	5%		
Height for age, %ile**	24		
Weight for age, %ile	44		

N=382

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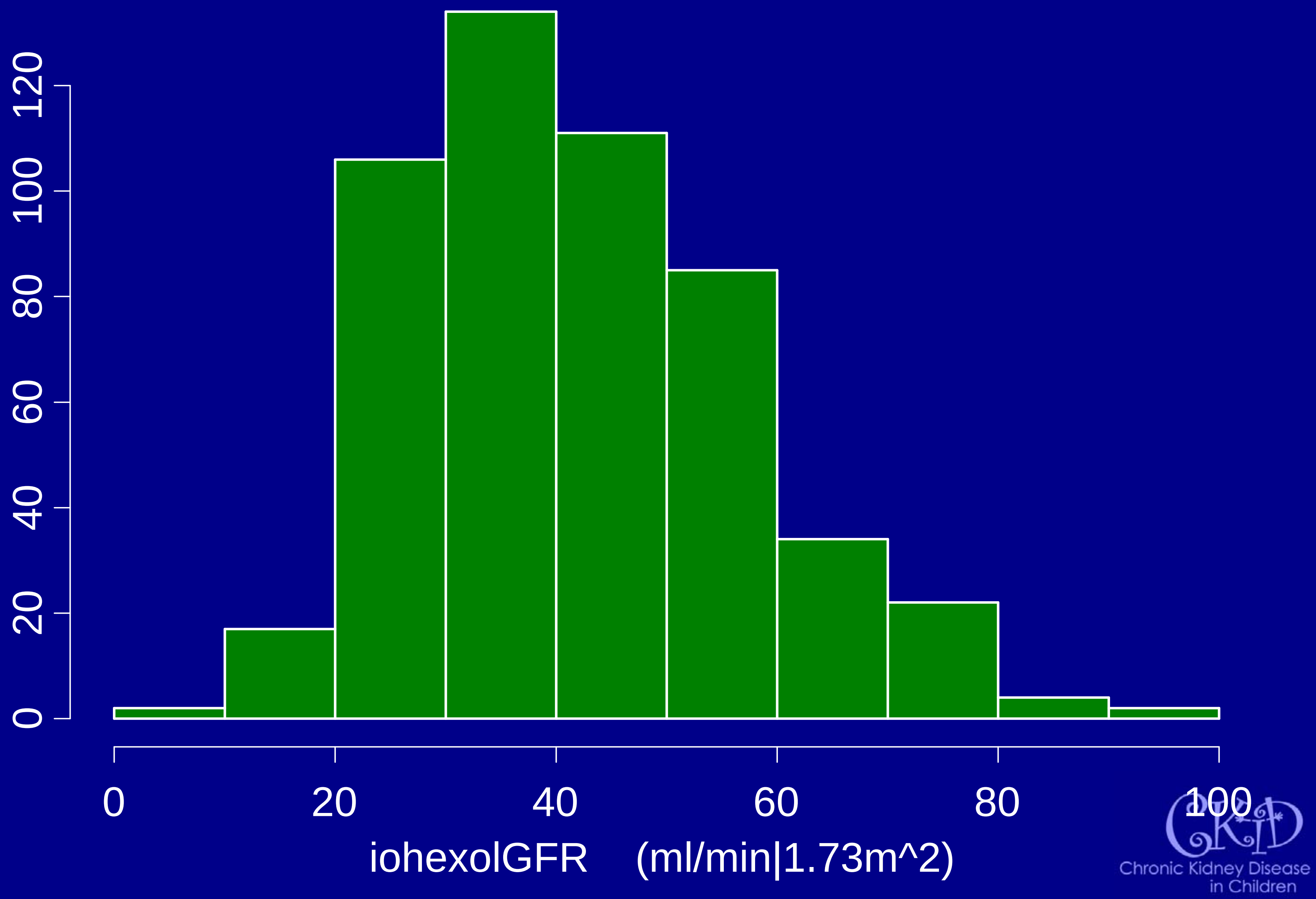
CKiD;   N= 517 Person-Visits; June 2007



Regression Coefficients and R^2; all variables in the log scale. N=514

	DEPENDENT VARIABLE	
	BSA-UNADJUSTED GFR: I/AREA	BSA-ADJUSTED GFR: (I/AREA) (1.73/BSA)=iGFR
VARIABLES		
Male	-0.025; <1%	-0.019; <1%
Age	0.570; 32%	-0.066; 1%
Weight	0.056; 48%	-0.012; <1%
Height	1.667; 39%	-0.136; <1%
BSA	0.970; 47%	-0.030; <1%
1/SCr	0.166; 2%	0.566; 49%
Ht / SCr	0.653; 24%	→ 0.776; 65%
1/Cystatin	0.862; 20%	1.012; 58%
1/BUN	0.471; 17%	0.530; 41%

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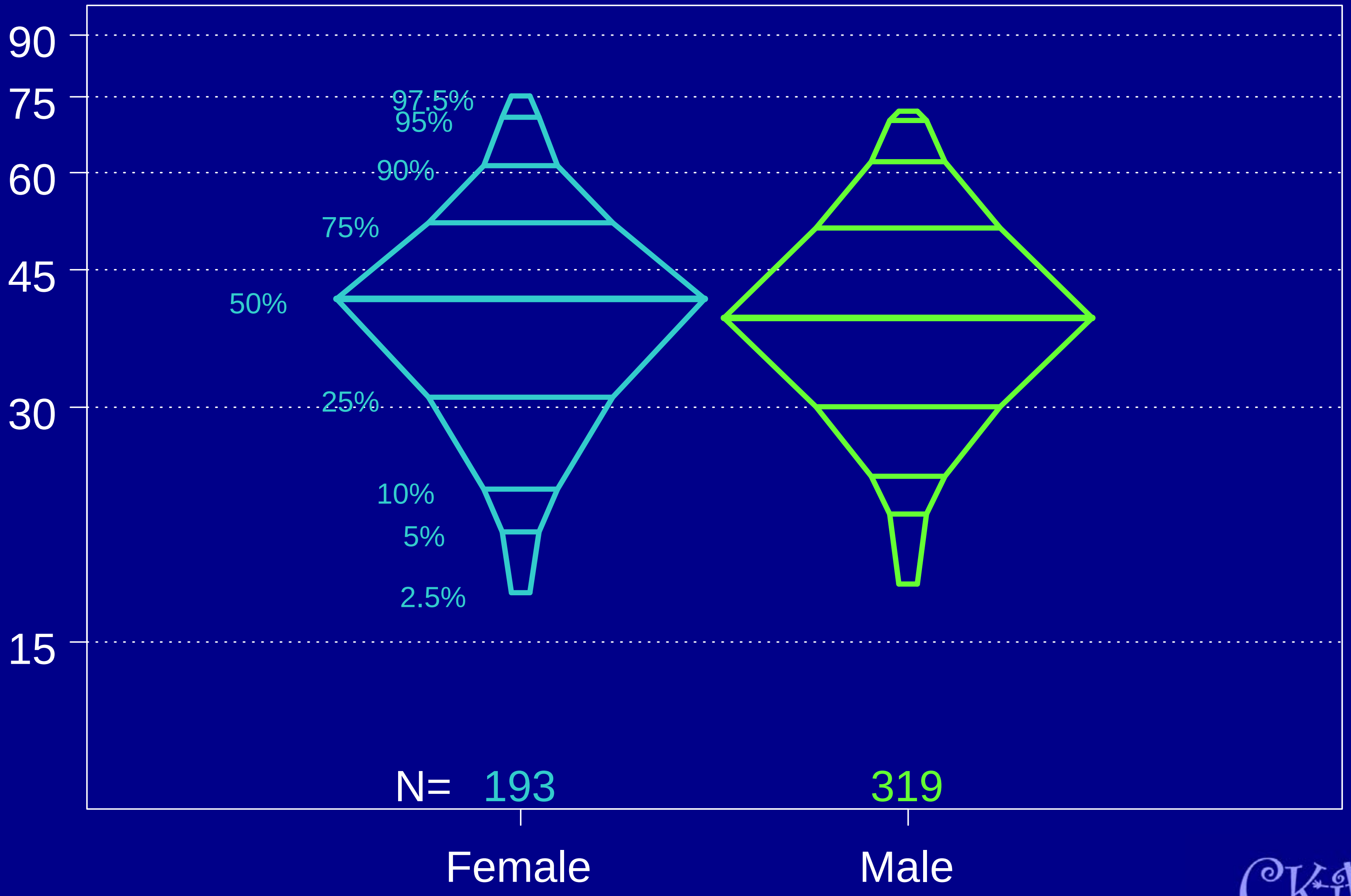
iohexol GFR; CKiD



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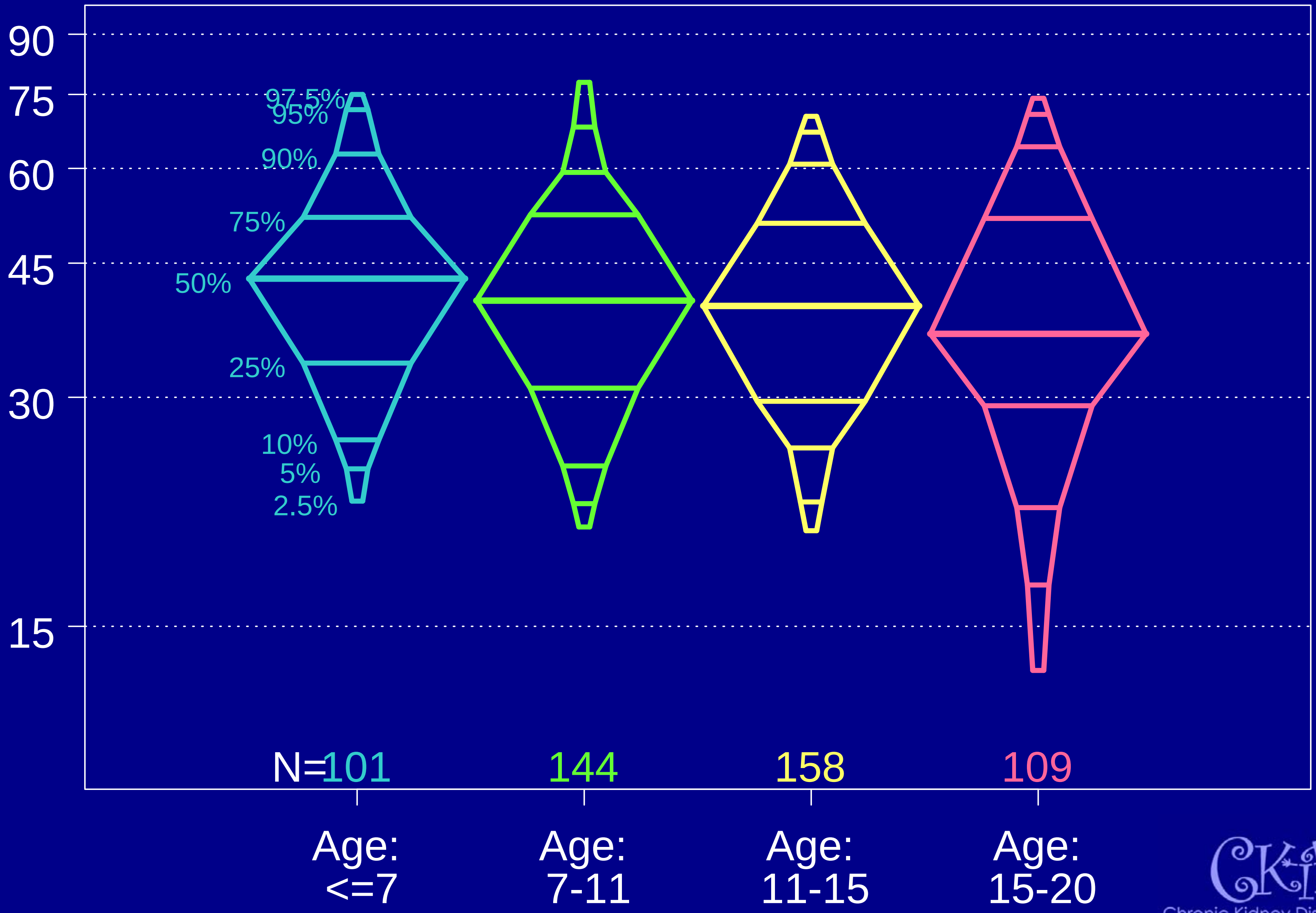
iohexol GFR; CKiD



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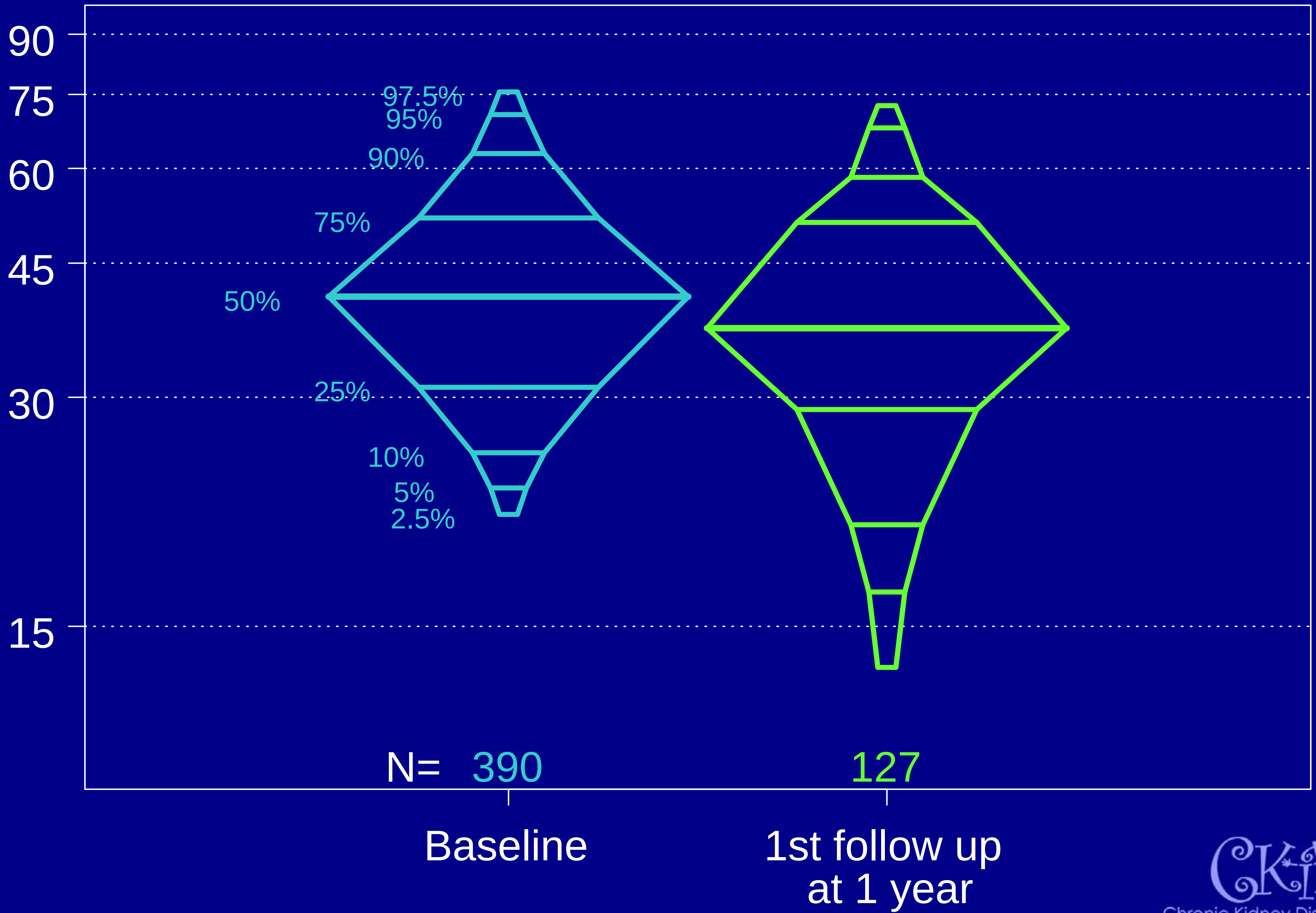

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Equation to estimate GFR

- Original Schwartz estimation of GFR showed a dependence on Ht/Scr.
- Blood urea nitrogen (BUN, end product of protein metabolism) concentration tends to vary inversely with GFR and urea clearance is ~1/3-2/3 of GFR.
- Cystatin C (cysteine proteinase inhibitor) has been proposed to be a good estimate of GFR.

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Descriptive Statistics (N=482 P-Visits*)

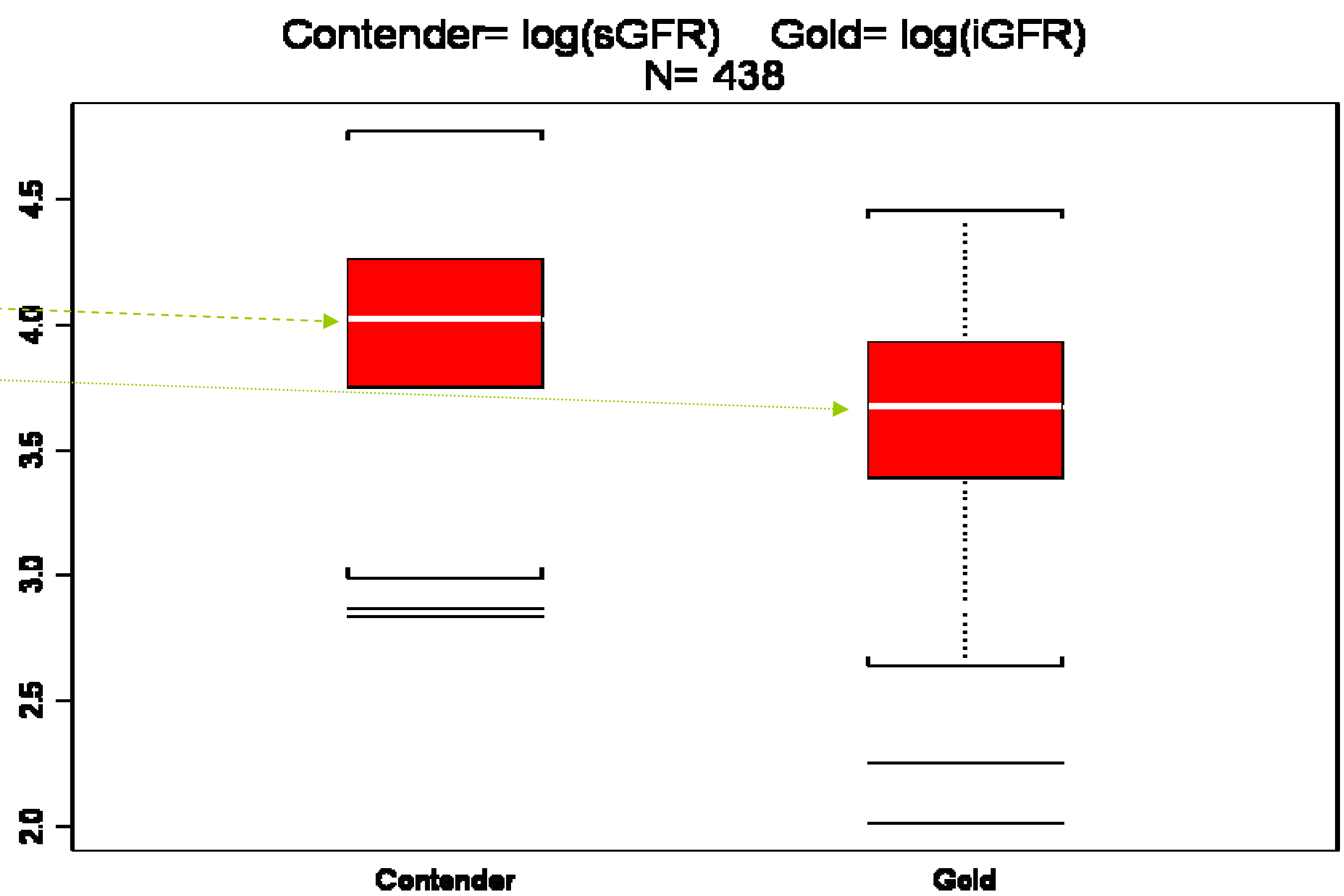
	Mean	Std. Deviation
iGFR	41.5	14.8
Height (m)	1.38	0.25
SCr	1.60	0.82
Ht/SCr	1.01	0.38
Age	10.9	4.2
Weight (kg)	40.9	21.7
BUN (N=459)	33.2	15.1
Cystatin C (N=238)	1.89	0.52
% female	37%	--

*Excluded: if t120 <80 min or based on a GFR2 with crossvalidated concentrations

Original Schwartz Formula Overestimates GFR CKiD Study

sGFR 55

iGFR 41

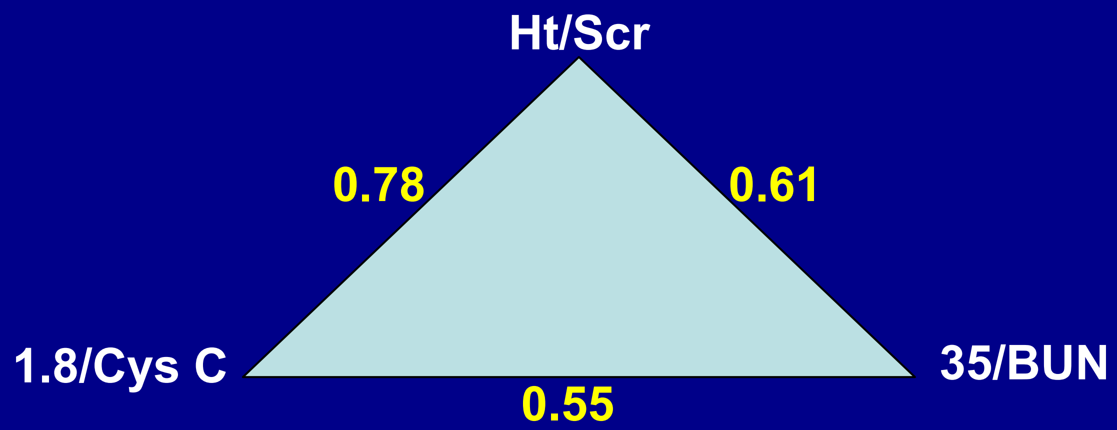


Correlation = 0.788

Correlation Coefficients*

	Ht/SCr	35/BUN	1.8/Cystatin C
iGFR	0.81	0.63	0.76

Correlations among Predictors



* All variables in the log scale and all correlation coefficients significant at the α = 0.05 level

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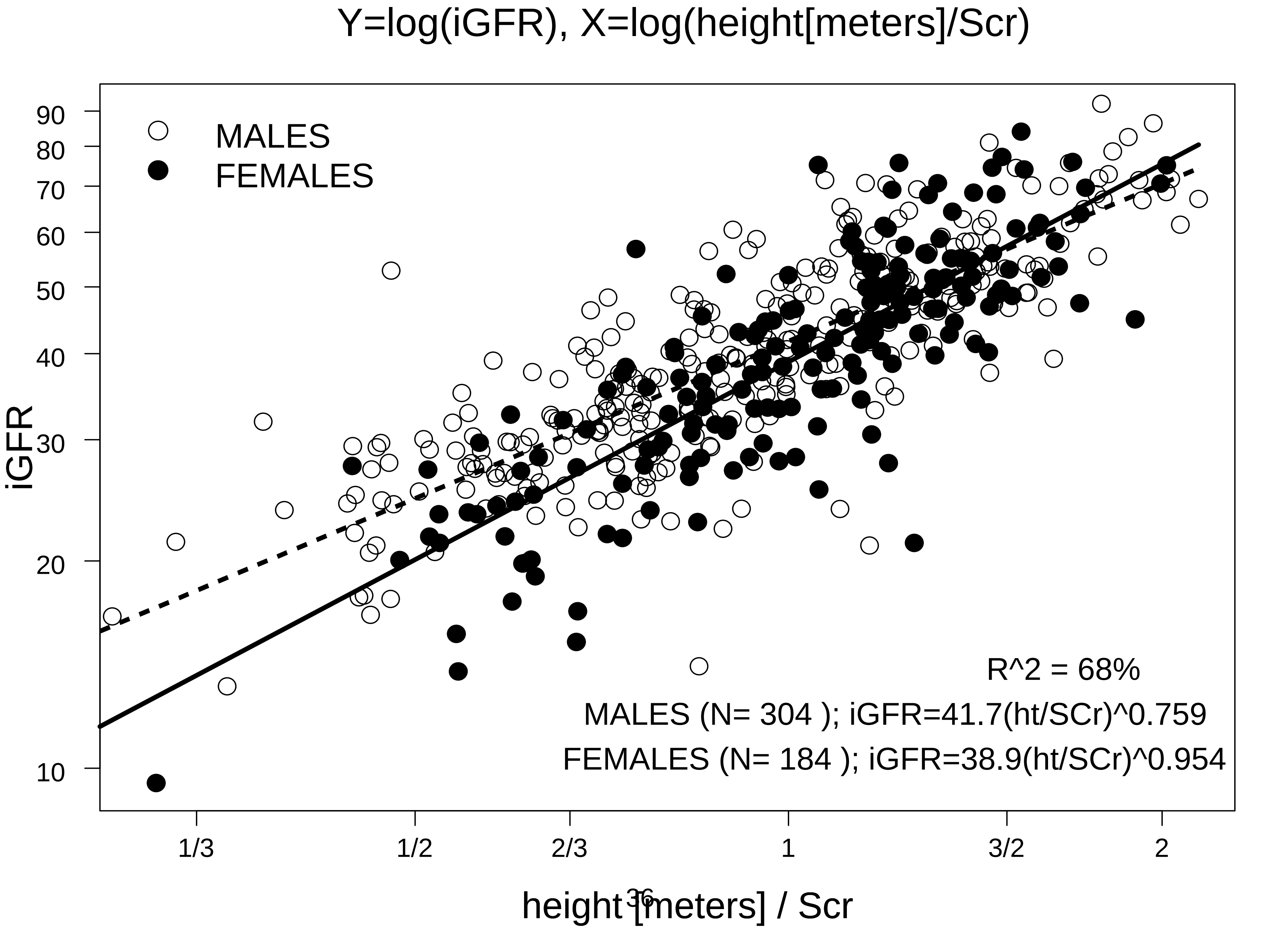
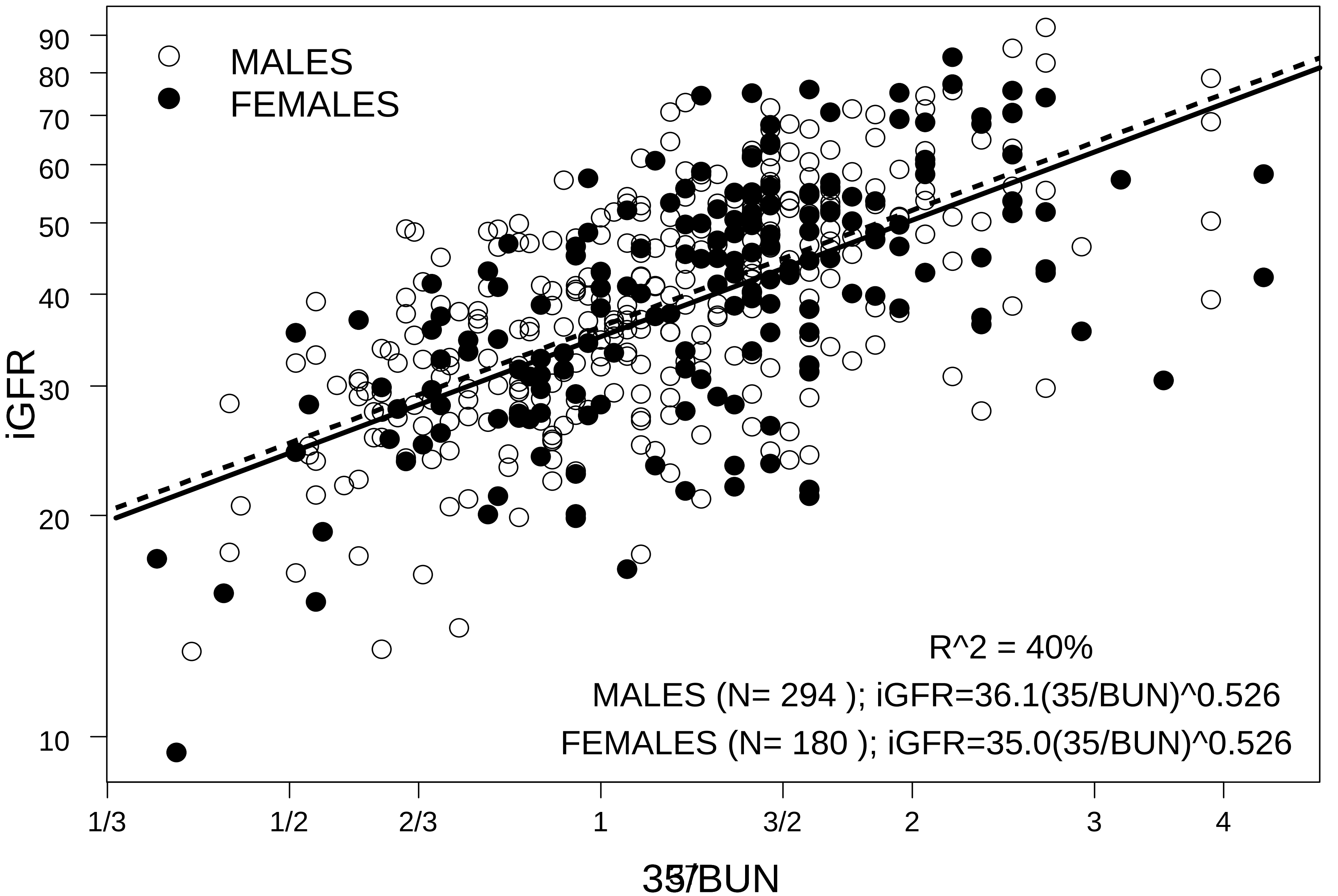
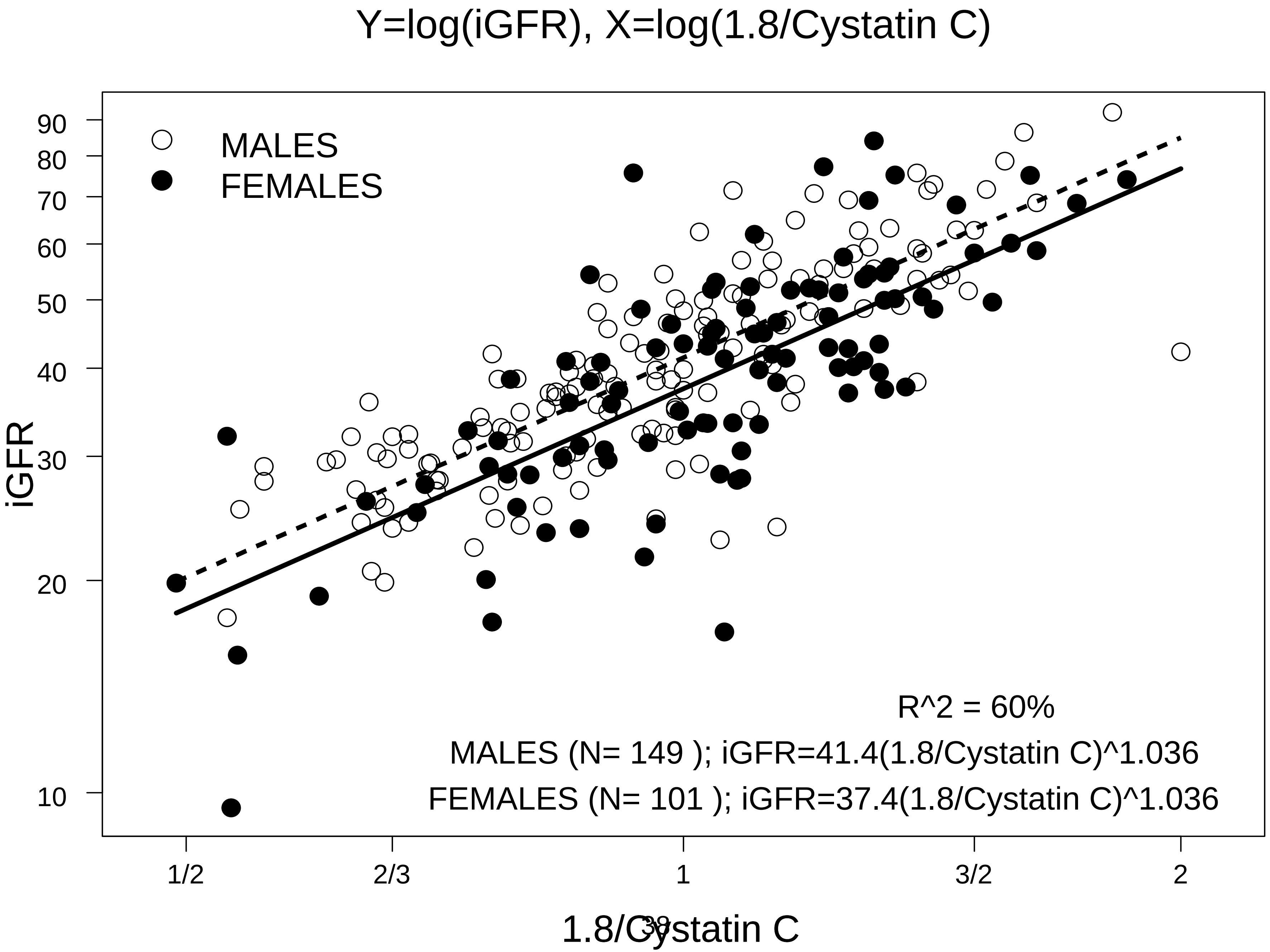

Y=log(iGFR), X=log(height[meters]/Scr)
MALES
FEMALES
R^2 = 68%
MALES (N= 304); iGFR=41.7(ht/SCr)^0.759
FEMALES (N= 184); iGFR=38.9(ht/SCr)^0.954
iGFR
90
80
70
60
50
40
30
20
10
1/3
1/2
2/3
1
3/2
2
height [meters] / Scr

Y=log(iGFR), X=log(35/BUN)





Y=log(iGFR), X=log(1.8/Cystatin C)
MALES
FEMALES
90
80
70
60
50
40
30
20
10
iGFR
R^2 = 60%
MALES (N= 149); iGFR=41.4(1.8/Cystatin C)^1.036
FEMALES (N= 101); iGFR=37.4(1.8/Cystatin C)^1.036
1/2
2/3
1
3/2
2
1.8/Cystatin C

$$eGFR = a\left[\frac{height}{SCr}\right]^{b}\left[\frac{35}{BUN}\right]^{c}\left[\frac{1.8}{Cystatin}\right]^{d}$$

Equation*	Description		a	b	c	d	R^2
I	updated Schwartz		41.2	1	0	0	55%
II	Gender-specific	Girls	38.9	0.95	0	0	
	height (m) / SCr	Boys	41.7	0.76	0	0	68%
III	II + BUN	Girls	37.4	0.81	0.18	0	
		Boys	40.1	0.64	0.18	0	70%
IV	III + Cystatin	Girls	36.6	0.58	0.14	0.45	
		Boys	40.9	0.37	0.14	0.45	74%

*Prediction of each equation significantly ($p<0.001$) better than previous equation.

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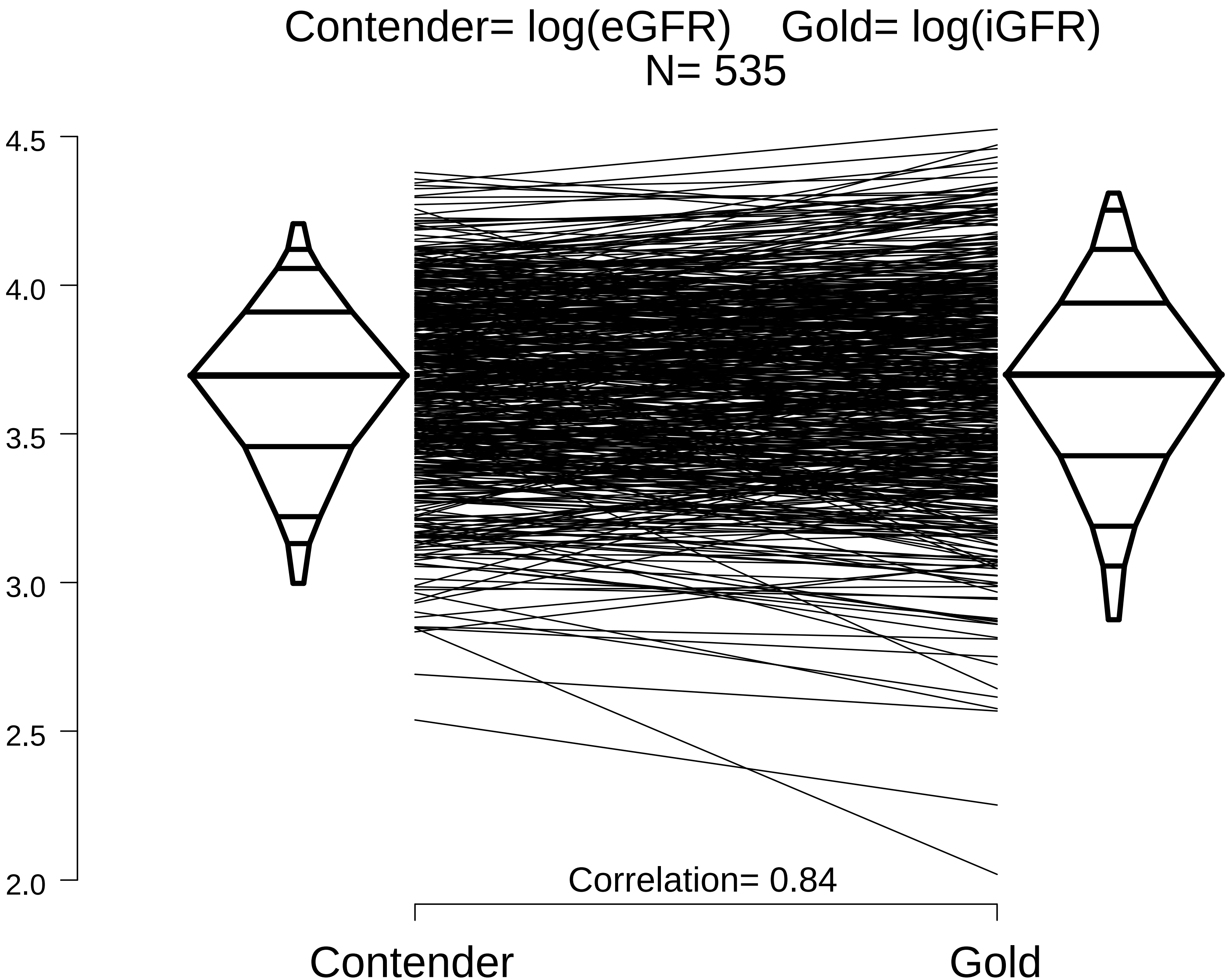
Contender= log(eGFR)   Gold= log(iGFR)
N= 535
4.5
4.0
3.5
3.0
2.5
2.0
Correlation= 0.84
Contender
Gold

Conclusions

- **CKiD data are useful for providing GFR estimating equations (I, II, III, and IV).**
- **The updated classic Schwartz formula has limitations but can be used for a quick approximation of GFR at the bed side.**
  - **For ht in cm: eGFR = 0.4(ht/Scr).**
- **Multivariate gender-based equations (III and IV) incorporating BUN and Cystatin C are significantly better for predicting GFR.**
- **Multivariate prediction equations will be instrumental for estimating GFR in the CKiD study when an iohexol-based GFR is not performed (at the V3 visit).**
- **Prediction equations would be considerably enhanced by the addition of ~100 children with eGFR>100 ml/min per 1.73 m^2.**

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