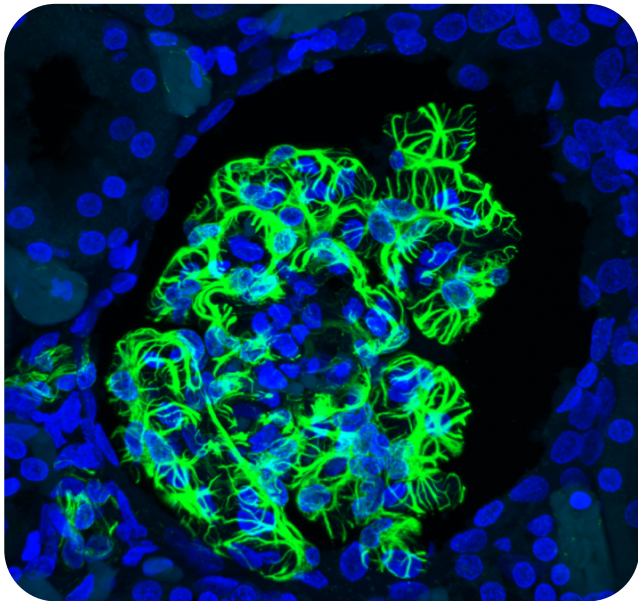# Nephron Number and Function in Disease

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Human Nephrogenesis and Nephron Endowment at Birth

Nephrogenesis begins in week 9 of human gestation, and ends at approx. week 36.

Nephron endowment is set shortly before term birth, and therefore any deficit is permanent.

Strong correlation between increased birth weight and increased nephron number in adults – 230,000 more nephrons/kg birth weight *(Hughson et al. Kidney Int 2003).*

Children born preterm or small for gestational age have low nephron endowment and increased risk for adult hypertension and CKD *(Rodriguez et al. Ped Nephrol 2005; Abitbol and Rodriguez Nat Revs Nephrol 2012).*

Nephron endowment in children and nephron number in adults varies widely.
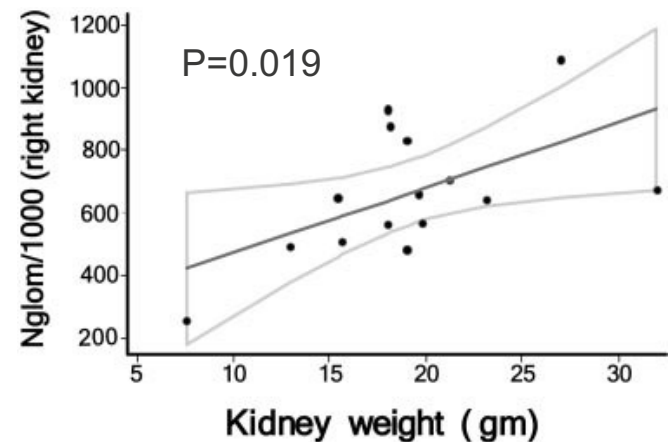
Zhang et al. JASN 2008

4.5-fold range in nephron number in 15 children <3mo

Nephron Number in Adults = Nephron Endowment Minus Nephron Loss

<25 studies, mostly small samples, all require biopsy/autopsy tissue

Table 3. Estimated nephron number per kidney in adults across different studies

Study Population	Clinical Kidney Disease Present	Technique	Mean Nephron No. per Kidney	Sample Size	Clinical Characteristics Associated with Low Nephron Number	Year of Publication
Autopsy series						
Traumatic accidents	no	Acid maceration	908,333	18	Age	1973[43]
Autopsy cases	no	Acid maceration	1,309,280	32	Age	1977[44]
Autopsy of full term infants	no	Acid maceration	1,107,000	28	Low birth weight, low vitamin A levels	1999[21]
Autopsy cases	no	Disector/fractionator	617,000	37	Age	1992[6]
Traumatic accidents	yes	Disector/fractionator	702,379	10	Hypertension	2003[8]
	no		1,429,200	10	N/A	
Autopsy cases	no	Disector/fractionator	992,353	39	N/A	2010[11]
Autopsy cases	no	Disector/fractionator	901,902	420	Age, low birth weight, short height, Australian Aboriginal race, hypertension	2010[22]
Autopsy cases	some	MRI with cationized ferritin	1,236,667	3	N/A	2014[38]
Living patients						
Stable renal transplants	some	MRI and protocol biopsy (Weibel–Gomez model)	730,000	39	Age, low GFR	2003[18]
Older and younger kidney donors	no	Whole-kidney K_f	631,500	34	Age, low GFR	2010[15]
Healthy kidney donors	no	Whole-kidney K_f	641,730	19	Age	2015[16]
Normotensive and hypertensive kidney donors	no	Whole-kidney K_f	605,592	51	Age, hypertension	2015[17]
Healthy kidney donors	no	Renal CT angiogram and implantation biopsy (Weibel–Gomez model)	873,696	1638	Age[a] female sex, short height[a] family history of ESRD[a] high serum uric acid[a] and low GFR[a]	This study

MRI, magnetic resonance imaging.

[a]Characteristic was an independent predictors of low nephron number in the study.
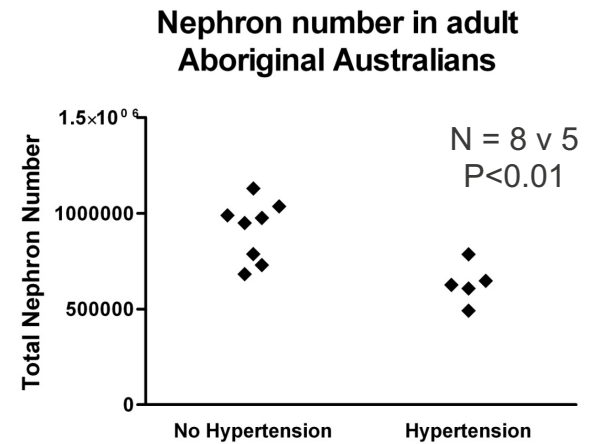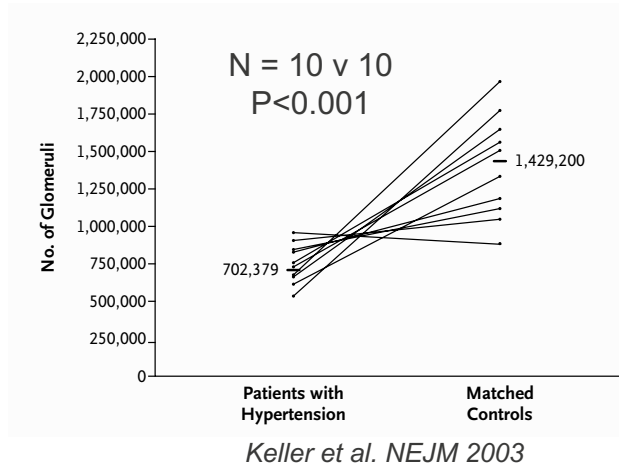
Denic et al. JASN 2017

Large Range in Nephron Number in Normal Kidneys

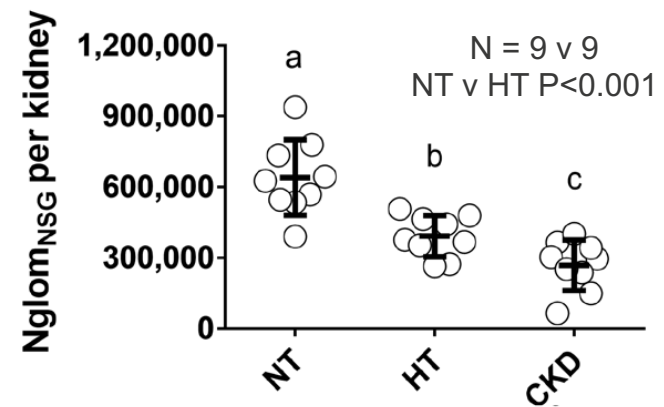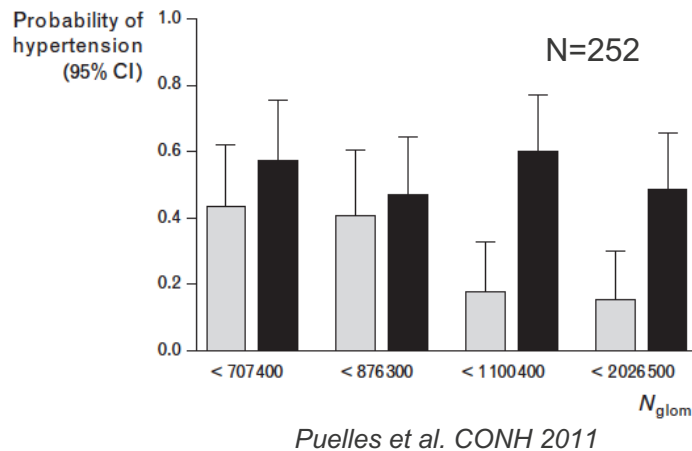|	Population	N	Mean	Range	Fold-Variation
Nyengaard & Bendtsen *Anat Rec 1992*	Danish	37	617,000	331,000 - 1,424,000	**4.3**
Merlet-Bénichou et al. *Lab Invest 1999*	French	28	1,107,000	655,000 - 1,554,000	**2.4**
Keller et al. *NEJM 2003*	German normotensive	10	1,429,200	884,458 - 1,959,914	**2.2**
Bertram et al. *Ped Nephrol 2011*	Caucasian Americans	147	924,981	227,327 - 1,956,973	**8.6**
Bertram et al. *Ped Nephrol 2011*	African Americans	190	904,864	210,332 - 2,702,079	**12.8**
Hoy et al. *Kidney Int 2006*	Australian non-Aborigines	24	861,541	380,517 - 1,493,665	**3.9**
Hoy et al. *Kidney Int 2006*	Australian Aborigines	19	713,209	364,161 - 1,129,233	**3.1**
McNamara et al. *NDT 2008, NDT 2010*	Senegalese Africans	47	988,263	536,171 – 1,764,421	**3.3**
Kanzaki, Puelles et al. *JCI Insight 2017*	Japanese – normotensive	9	666,140	419,282 - 960,756	**2.3**

Human Nephron Number, Hypertension and Renal Pathophysiology

- Relatively few studies to date due to current need for kidney tissue (biopsy/autopsy)

- Most studies have relied on surrogate markers of nephron number

  - Low birth weight
  - High birth weight
  - Preterm birth
  - Being born small for gestational age
  - Reduced kidney volume on ultrasound
  - Enlarged glomeruli on kidney biopsy

Human Nephron Number and Hypertension

N = 10 v 10
P<0.001

1,429,200

702,379

Patients with Hypertension / Matched Controls

Keller et al. NEJM 2003

Nephron number in adult Aboriginal Australians

N = 8 v 5
P<0.01

No Hypertension / Hypertension

Hoy et al. Kidney Int 2006

N=252

Probability of hypertension (95% CI)

N_{glom}

< 707400   < 876300   < 1100400   < 2026500

Puelles et al. CONH 2011

N = 9 v 9
NT v HT P<0.001

a   b   c

NT   HT   CKD

Kanzaki, Puelles et al. JCI Insight 2017

Nephron Number and Renal Pathophysiology

Low nephron number associated with increased glomerulosclerosis (*Douglas-Denton et al. Ethnic Dis 2006; Hughson et al. Kidney Int 2006; McNamara et al. NDT 2008; Denic et al. JASN 2017*)

Low nephron number associated with increased nephrosclerosis (*Hughson et al. Kidney Int 2006; Denic et al. JASN 2017*)
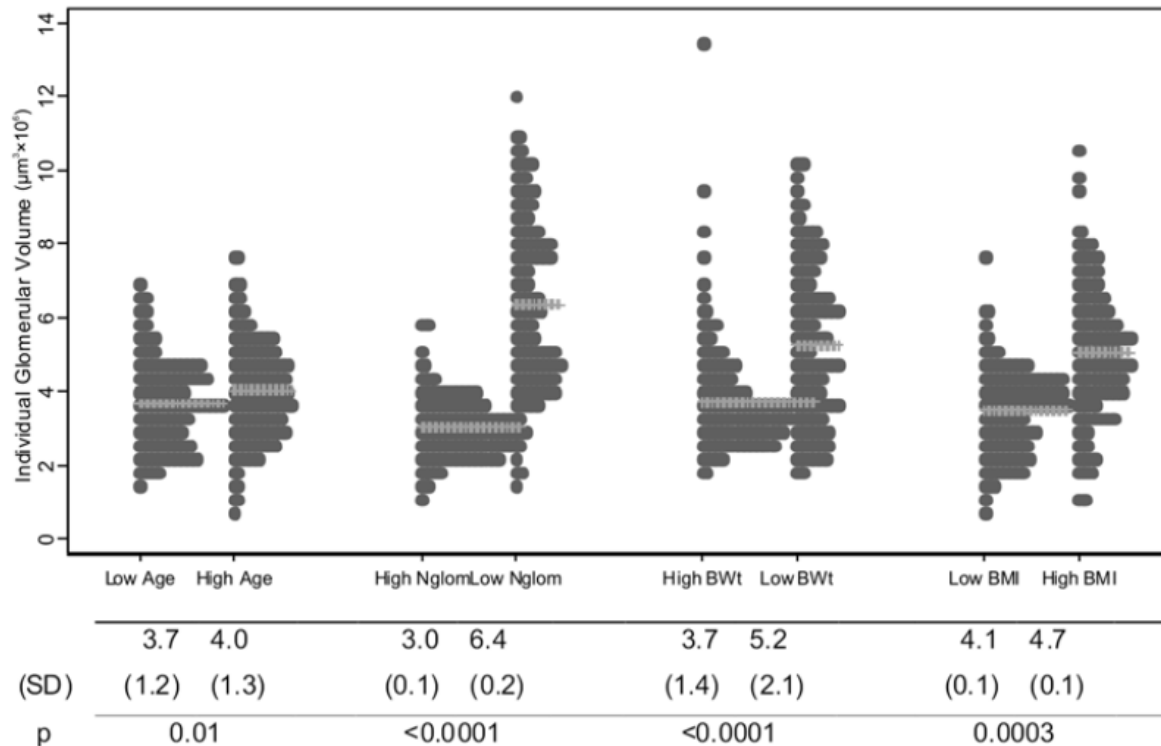
Low nephron number associated with low measured and estimated GFR and SNGFR (*Fulladosa et al. JASN 2003; Tan et al. JASN 2009, Kidney Int 2010; Denic et al. JASN 2017; Kanzaki, Puelles et al. JCI Insight 2017*)

Numerous studies showed birth weight inversely associated with microalbuminuria, decreased GFR, FSGS and ESKD.

Kanzaki, Puelles et al. JCI Insight 2017

MONASH University
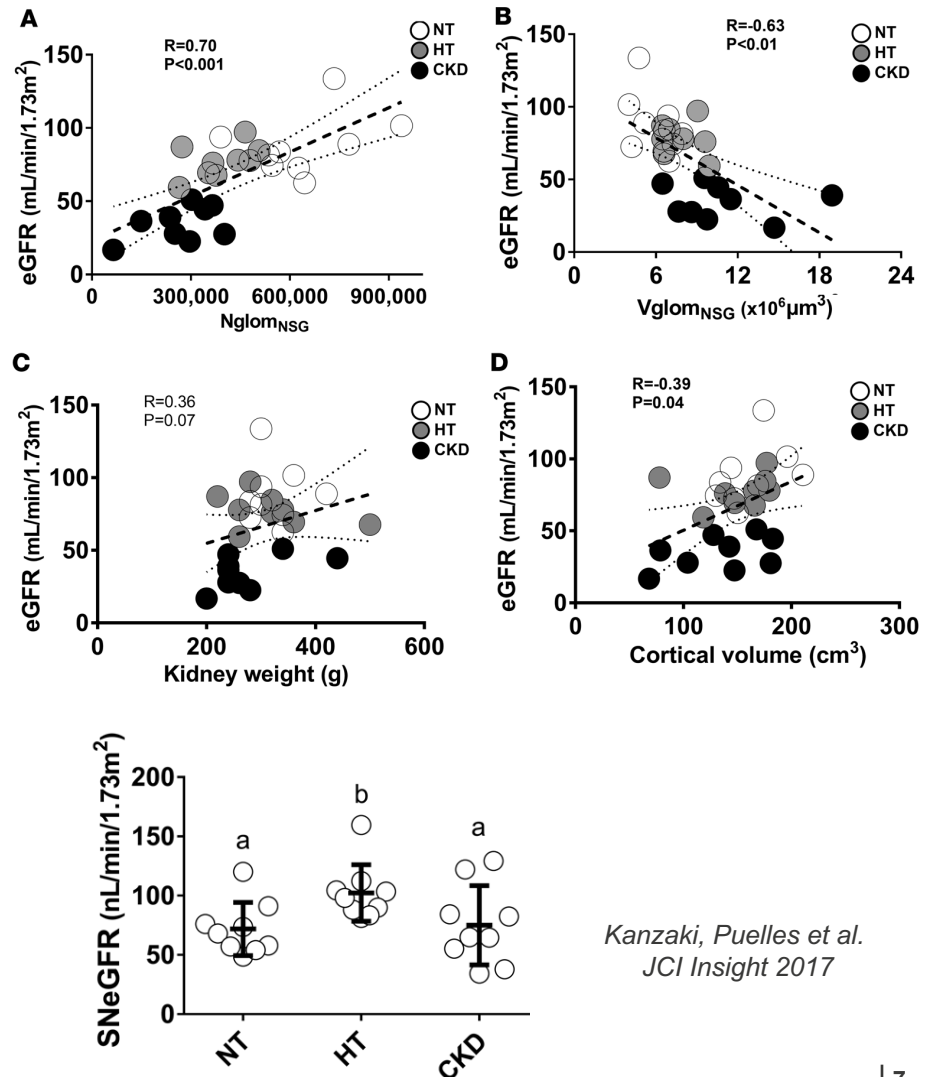
Towards the Glomerular Size Distribution for a Whole Kidney

(US white males; 6 subjects/group, 30 gloms/subject - 1,440 gloms; Cavalieri)

	Low Age	High Age		High Nglom	Low Nglom		High BWt	Low BWt		Low BMI	High BMI
	3.7	4.0		3.0	6.4		3.7	5.2		4.1	4.7
(SD)	(1.2)	(1.3)		(0.1)	(0.2)		(1.4)	(2.1)		(0.1)	(0.1)
p	0.01			<0.0001			<0.0001			0.0003	

Hoy et al. Clin Nephrol 2010

Why Estimate Glomerular Number and Size *In Vivo*?

Obtain a measure of functional nephron/glomerular mass.

Enable more accurate estimation of SNGFR.

Estimate functional nephron mass in patients newly-diagnosed with CKD – baseline value.

Determine the effectiveness of therapy in patients with CKD – progression rates, is nephron mass stabilised or decreasing? What is happening to SNGFR?

Count/size perfused (non-sclerosed) and non-perfused (sclerosed) glomeruli.

Better understand temporal relationships between decreasing nephron number and changes in blood pressure, GFR and pathology

In animal studies, perform longitudinal studies on effects of potential new therapies on glomerular number, size and SNGFR.

Estimate nephron number in children born small or premature and identify those to monitor closely (proteinuria, blood pressure). Detect problems early and treat accordingly.

Summary

Reports of human nephron (glomerular) number

- <25 studies to date – we have a lot to learn
- Only approx. 10 racial groups studied to date
- Generally small samples
- All used kidney tissue

Nephron number

- Varies >10-fold in normal human kidneys – some of this variation present at birth
- Is lower in premature and low birth weight babies
- Is lower in some racial groups than others
- Low nephron number is often associated with
    - hypertension
    - lower estimated and measured GFR
    - glomerulosclerosis, cortical fibrosis, nephrosclerosis

COLLABORATORS

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