CHAPTER

2 Clinical Importance of Nephron Mass

Valerie A. Luyckx • Thomas F. Mueller

INTRODUCTION

The relationship between renal salt handling, intravascular volume homeostasis, and hypertension is well established, which points to the kidney as the central organ in the development of hypertension.[1] Based on the concept of developmental programming, where an environmental stimulus experienced during a critical period of early development can induce long-term structural and functional adaptive changes in the developing organism, Brenner et al. proposed that a low nephron number, acquired during fetal life, may predispose an individual to hypertension and renal disease.[2,3] This hypothesis was attractive because low birth weight, a marker of an adverse intrauterine environment, if associated with a congenital reduction in nephron number, could potentially explain the variability in hypertension and renal disease prevalence observed among populations of different ethnicity where those with lower birth weights tend to have a higher burden of renal disease.[4–7] The initial hypothesis suggested that a kidney with fewer nephrons would have a reduced filtration surface area with a limited capacity to excrete sodium, thereby contributing to the development of hypertension. Although this "nephron number" hypothesis was initially quite controversial, and with time has proved to be not entirely this straightforward, the association between nephron number and predisposition to hypertension and renal disease has been borne out in many animal experiments and human studies.[8–12] In this chapter we put forward the existing evidence comprising animal and human studies, which link nephron mass, birth weight, and other clinical variables with clinical outcomes. Extrapolation from animals to humans has many limitations and, therefore, where possible we have included human studies to corroborate or refute animal findings. Although this field has grown significantly within the last decade and many questions remain unanswered, a clearer and consistent picture is emerging that shows nephron mass does have clinical importance.

An individual's nephron mass is determined by a complex interplay between genetics and environment, evolving throughout their lifetime, bearing the imprint of their past, being reflected in their present, and affecting their future risk of hypertension and renal disease. Although traditionally it has been thought that all kidneys have about 1 million nephrons, recent studies have found that total glomerular number varies up to 13-fold in human kidneys, much more, for example, than height or weight (Table 2.1).[13] The terms "nephron endowment," implying number of nephrons present upon completion of nephrogenesis; "nephron number," implying the number of intact nephrons at the time of measurement; and "glomerular number," including the number of tubular and atubular glomeruli, have all been used interchangeably.[13] In this chapter we use the term "nephron number" more generally to describe the total number of nephrons in a kidney at the time of discussion. The term nephron mass is used more broadly as a clinical term to incorporate nephron number, kidney weight, kidney size, and kidney volume. A discussion of the importance of acquired reduction in nephron mass in later life is beyond the scope of this chapter.

DEVELOPMENTAL DETERMINANTS OF NEPHRON NUMBER

Low Nephron Number

Kidney development in humans proceeds from the 9th to the 36th week of gestation.[9,14] Accurate determination of nephron number is difficult because nephron number cannot be determined in humans in vivo. The unbiased fractionator-sampling/dissector method is thought to be the most objective nephron counting method, and is currently utilized in most human studies.[15,16] This method, however, requires postmortem kidney samples and is very labor intensive. An in vivo glomerular counting method comparing the fractionator technique with a combined renal biopsy/magnetic resonance imaging (MRI) method in explanted canine kidneys has been attempted.[17] This study found a good correlation of glomerular number on average between the two methods, but, within kidneys, there was a 36% variance, calling individual applicability into question. Large-scale human

2.1 Nephron Numbers in Humans

Reference	Population	Sample Size	Mean	Range	Fold
Nyengaard and Bendtsen	Danish	37	617,000	331,000–1,424,000	4.3
Merlet-Benichou et al.[a]	French	28	1,107,000	655,000–1,554,000	2.4
Keller et al.	German	20	1,074,414	531,140–1,959,914	3.7
	Hypertensive	10	702,379	531,104–954,893	1.8
	Normotensive	10	1,429,200	884,458–1,959,914	2.2
Douglas-Denton et al.	African Americans	105	884,938	210,332–2,026,541	9.6
	White Americans	84	843,106	227,327–1,660,232	7.3
Hoy et al.	Australian non-Aborigines	21	861,541	380,517–1,493,665	3.9
	Australian Aborigines	19	713,209	346,161–1,129,223	3.1
McNamara et al.[b]	Senegalese	47	992,353	536,171–1,764,241	3.3
Hoy et al.	African and white Americans, Australian Aborigines, and non-Aborigines and Senegalese	420	901,902	210,332–2,702,079	12.8

[a]Used acid maceration technique. All other studies used unbiased stereology.
[b]Values for 47 participants were combined from two publications.
Reprinted with permission from Puelles VG, Hoy WE, Hughson MD, et al. Glomerular number and size variability and risk for kidney disease. Curr Opin Nephrol Hypertens. 2011;20:7–15. See original manuscript for detailed references.

studies of nephron number and association with phenotype are therefore not easily feasible.

Average nephron number has been reported to range from 617,000 (range 331,000–1,424,000) to 1,429,200 (range 884,485–1,959,914) per kidney among normal adult Caucasian Europeans.[10,18] Other studies including subjects of multiple ethnic origins from the United States, Africa, and Australia showed somewhat similar results, with a mean number around the mid 800,000 glomeruli per kidney, with a very wide range, from 210,332 to 2,702,079 as shown in Table 2.1.[13] The range appears widest in kidneys from subjects of African origin.[13,19] In general, nephron numbers are lower in older subjects, attributed to age-related glomerulosclerosis and obsolescence.[18,20] Whether the high variability in nephron number across populations reflects true differences or is confounded by small sample sizes or limitations of counting methods will become clearer with time as more studies accumulate or as better techniques evolve.

Various animal models have been used to study the impact of developmental programming on nephrogenesis. The details and pathophysiology of these models, and mechanisms whereby nephron numbers are reduced, are beyond the scope of this chapter and are outlined in detail elsewhere.[8,21,22] Extrapolating from the animal studies, from a clinical point of view, the factors associated with development of low nephron number can be divided into two groups: modifiable and nonmodifiable, as outlined in Table 2.2.

Modifiable Factors

Modifiable factors associated with low nephron number include prenatal events—factors occurring during gestation and postnatal events occurring in the neonate.

Prenatal Factors. Maternal diets deficient in protein, total calories, or iron have all been shown to reduce nephron numbers in offspring of experimental animals, most often in association with low birth weight.[12,23–26] Figure 2.1 shows a reduction in nephron numbers in low birth weight rats that were subjected to maternal low protein diets during gestation. Maternal dietary deficiencies are common in pregnant mothers in developing countries and therefore likely clinically relevant in a large proportion of the world.[27] Maternal vitamin A deficient diets are associated with a dose-dependent reduction in nephron number in animals.[28]

2.2 Factors Associated with Charges in Nephron Number and Kidney Size

REDUCED NEPHRON NUMBERS OR KIDNEY SIZE

Timing	Condition	Source of Data	Effect on Nephron Number (NNx)/Kidney Size	References
Prenatal, modifiable	Maternal low protein diet or total calorie restriction	Animal	↓ NNx, 16%–40%	12, 246
	Maternal vitamin A restriction	Animal	↓ NNx, in proportion to reduction in vitamin A	28, 29
		Human	Small infant kidney size	
	Maternal iron restriction	Animal	↓ NNx, 22%	25
	Gestational glucocorticoid exposure	Animal	↓ NNx, 20%–38%	37, 180
	Uterine artery ligation/ embolization	Animal	↓ NNx, 20%–30%	81
	Maternal diabetes/ hyperglycemia	Animal	↓ NNx, 10%–35%	50, 51, 247
	Gestational drug exposure	Animal		
	■ Gentamicin		↓ NNx, 10%–20%	40–45, 248
	■ β lactams		↓ NNx, 5%–10%	
	■ Cyclosporine		↓ NNx, 25%–33%	
	■ Ethanol		↓ NNx, 10%–20%	
	■ COX2 inhibitors		↓ NNx	
	■ Indomethacin		↓ NNx	
Prenatal, nonmodifiable	Genetics			
	■ RET(1476A) polymorphism	Human	10% ↓ newborn kidney volume	63, 64
	■ PAX2 AAA haplotype	Human	10% ↓ newborn kidney volume	
	Prematurity	Human	NNx ↓ with gestational age, limited post natal nephrogenesis	54, 69, 132
			Reduced kidney size in growth restricted children	
Postnatal	Nutrition	Animal	NNx ↓ with postnatal nutrient restriction alone	32
	Renal failure	Human	? cause or consequence of NNx ↓	54

NORMALIZATION OR INCREASE IN NEPHRON NUMBER

Timing	Condition	Source of Data	Effect on Nephron Number (NNx)/Kidney Size	References
Prenatal	Maternal vitamin A supplementation	Animal	Normalization of NNx in LPD model	82
	Maternal amino acid supplementation	Animal	Normalization of NNx in LPD model	24

(continued)

2.2 Factors Associated with Charges in Nephron Number and Kidney Size (continued)

Timing	Condition	Source of Data	Effect on Nephron Number (NNx)/Kidney Size	References
	Ouabain administration	Animal	Normalization of NNx in LPD model	84
	Maternal uninephrectomy	Animal	NNx ↑	88, 89
	Genetics			
	■ ALDH1A2rs7169289(G) allele	Human	22% ↑ newborn kidney size	83
Postnatal	Reinstitution of good nutrition	Animal	Catch-up of NNx in LPD model	81
	Overfeeding	Animal	NNx ↑ in normal birth weight rats	152

↑, increase; ↓, decrease; ?, unknown.
Adapted from Luyckx VA, Brenner BM. The clinical importance of nephron mass. J Am Soc Nephrol. 2010;21:898–910.

Vitamin A deficiency was examined in a cohort of Indian compared to Canadian mothers and found to be associated with significantly smaller newborn renal volume, which the authors suggest likely reflects lower nephron number.[29] Retinoic acid, the active metabolite of vitamin A, functions as a transcription factor regulating expression of Ret, a tyrosine kinase receptor critical for kidney development.[30] Interestingly, vitamin A levels are reduced by smoking and alcohol intake, both known to reduce birth weight.[31] Uteroplacental insufficiency, induced by uterine artery ligation late in gestation, also results in low offspring birth weight and low nephron number.[32,33] This model may share some similarities

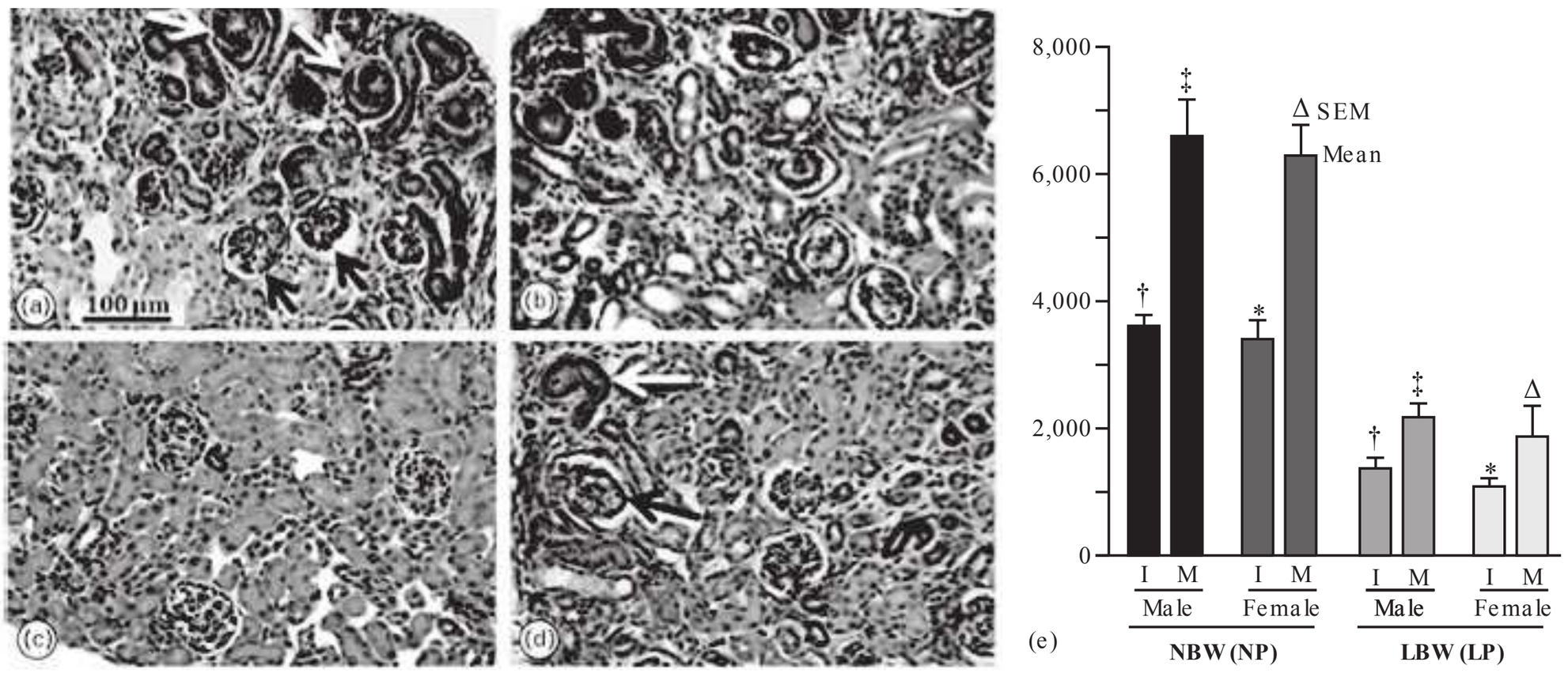

FIGURE 2.1 Relationship between glomerulogenesis, nephron number, and birth weight in rats subjected to maternal normal (NP) or low (LP) protein diets. Renal cortex at days 0 (d0) and 10 (d10) in rat offspring of NP-fed dams (normal birth weight, NBW) and LP-fed dams (low birth weight, LBW). *(a)* Normal glomerulogenesis in NBW offspring at d0, with comma-shape structure (immature renal corpuscle, *white arrow*) and inner vascularized structure (mature renal corpuscle, *black arrow*); *(b)* LBW d0 with fewer corpuscular structures and moderately dilated tubules; *(c)* NBW d10 showing only mature renal corpuscles; *(d)* LBW d10 showing immature and mature renal corpuscles; and *(e)* number of glomerulus-like structures (immature [I] and mature [M]) measured in NBW and LBW offspring ($n = 5$ per group). Symbols indicate group comparisons, $P < 0.05$. (Reprinted with permission from Villar-Martini VC, Carvalho JJ, Neves MF, et al. Hypertension and kidney alterations in rat offspring from low protein pregnancies. *J Hypertens Suppl.* 2009;27:S47–51.)

with preeclampsia in humans in terms of the reduction of uterine blood flow and the restriction of fetal nutrient supply.

Increased fetal glucocorticoid exposure is a likely mechanism whereby maternal low protein diet reduces nephron number, via reduced activity of placental 11β-hydroxysteroid dehydrogenase activity, shown in both animals and humans.[34,35] Similarly, administration of glucocorticoids during gestation in rats and sheep leads to reduced nephrogenesis, although this effect was not seen in the Marmoset monkey.[36–38] Glucocorticoids are thought to reduce nephron number by impacting ureteric bud invasion of the metanephric mesenchyme, thereby limiting branching morphogenesis.[8] The impact of maternal glucocorticoid utilization during pregnancy on human nephrogenesis is not known. Ingestion of other medications during pregnancy may also impact nephrogenesis in many ways.[39] Gestational administration of aminoglycosides, beta lactams, cyclosporine, cyclooxygenase inhibitors, and nonsteroidal anti-inflammatory drugs have all been associated with reduced nephron number in experimental models.[39–43] Similarly, chronic and acute gestational exposure to alcohol impairs embryonic ureteric bud branching, resulting in fewer nephrons in offspring.[44,45] In humans one abstract suggested an impact of maternal alcohol consumption on kidney development in Australian Aboriginal children.[9]

Conceivably, therefore, all of these prenatal experimental conditions may impact human nephrogenesis and minimization of these exposures prior to and during pregnancy would optimize fetal nephrogenesis. The timing of an insult during gestation is also relevant to its impact on nephrogenesis, with the greatest effect in animals generally seen with interventions in the latter half of gestation.[8]

Maternal factors also impact fetal development during gestation. Low birth weight is associated with multiple maternal factors although nephron number has not specifically been examined in most cases.[46,47] Manalich et al. found a strong correlation between low birth weight and low nephron number in a cohort of Cuban newborns.[48] Maternal hypertension and maternal smoking were correlated with low birth weight, although direct correlation with nephron number was not reported. In experimental animals, maternal diabetes or hyperglycemia has been shown to result in approximately 30% lower offspring nephron number in some, but not all, studies, although differences in methods of nephron number counting may account for some of the variability.[49–51] In other studies, maternal diabetes was associated with smaller kidneys, higher blood pressures, microalbuminuria, and reduced glomerular filtration rates in rat offspring.[51,52] In young adults, renal functional reserve was found to be reduced in those who had been exposed to maternal diabetes during gestation, compared to those with paternal diabetes (i.e., excluding a genetic component), or those with nondiabetic parents.[53] The reduced renal functional reserve was interpreted by the authors as a possible surrogate for a reduced nephron number acquired in utero in the offspring of diabetic mothers.

Postnatal Factors. Although nephrogenesis is thought to be complete at birth in humans, this may not be the case for babies born prematurely, and therefore a window in which nephrogenesis may still be vulnerable likely exists soon after birth in these infants.[54] Consistent with this possibility, early postnatal growth restriction alone in normal birth weight rats was associated with a reduction in nephron number, demonstrating the importance of early postnatal nutrition on nephrogenesis.[32] The relevance of these findings to the human, however, is questionable because nephrogenesis normally proceeds for 10 days after birth in rodents and therefore this period is analogous to late gestation in humans. These data may, however, have relevance to humans born prematurely. Indeed, in a cohort of children born either very low birth weight (<1,000 g) or premature (<30 weeks gestation), extrauterine growth restriction was associated with significantly lower glomerular filtration rates at a mean of 7.6 years of age, suggesting an impact of postnatal nutrition on renal development.[55] Another study of postmortem kidneys from premature infants who died after 40 days of life found glomerular number to be significantly lower in those who developed renal failure compared to those who did not. These findings may suggest that renal failure itself inhibits glomerulogenesis; however, it is also possible that fewer glomeruli made these extremely ill infants more susceptible to renal failure. In another cohort of critically ill premature infants, renal failure was a significant complication and associated with a high mortality, although not associated with birth weight.[56] In contrast, another study did find neonatal acute kidney injury to be an independent predictor of mortality in very low birth weight infants.[57] Prematurity itself is a recognized risk for renal failure in infants, and has been shown to be associated with increased risk of subsequent hypertension and chronic kidney disease (CKD).[58] Taking these human studies together, postnatal events do impact renal development in premature infants and may have potentially adverse short- and long-term consequences.

Nonmodifiable Factors

Nonmodifiable factors also impact nephrogenesis, and may occur in isolation or together with other potentially modifiable factors described previously (Table 2.2).

Genetics. Rare congenital and genetic abnormalities associated with abnormal kidney development manifest with renal dysfunction, often presenting very early in life.[11,59] Approximately 40% to 60% of childhood end-stage renal disease (ESRD) results from some form of congenital renal hypoplasia.[60] More subtle renal developmental abnormalities—which may not manifest as overt syndromes but, rather, with later life renal dysfunction—may well be the result of gene polymorphisms impacting nephron number. Renal hypoplasia and reduced nephron number have been described with full or partial deletion of over 25 genes in mice, which are reviewed in detail elsewhere.[13,21,61] The important steps in kidney development

include specification of the metanephric blastema from the intermediate mesoderm, formation of the ureteric bud and its outgrowth from the wolffian duct, and ureteric bud branching. Genes participating in specification of the metanephric blastema from the intermediate mesoderm include Odd-1, Eya 1 Pax 2, Wt-1, Six 1, Gdnf, and Sall 1, of which Odd-1 and Eya -1 are critical.[21,60] Genes regulating formation of the ureteric bud and its outgrowth from the wolffian duct include Pax2, Liml, Bmp4, and Gdnf. [21,60] Gdnf (glial cell-derived neurotrophic factor) signals through the Gfrα1 receptor and the c-Ret receptor tyrosine kinase and, during branching, morphogenesis is only expressed on the tips of ureteric branches, selectively inducing branching at this location.[21] Among the most important pathways impacting nephrogenesis, therefore, are Gdnf/Ret and Pax2. In mice, deletion of Gdnf and c-Ret leads to renal agenesis or severe hypoplasia.[21,60] Deletion of Pax2, the "master organizer" of renal development, is incompatible with life.[60] The impact of genetic polymorphisms in these pivotal genes has been studied in humans. Haploinsufficiency of the PAX2 gene causes the autosomal dominant renal coloboma syndrome, associated with significant reduction in nephron number and "oligomeganephronia."[60,62,63] Taking this finding further, looking for a more subtle impact in the wider population, Quinlan et al. found that the common AAA haplotype of PAX2, present in 18.5% of newborns in a Canadian cohort, was associated with reduced allele-specific mRNA expression in vitro, and a 10% reduction in newborn kidney volume, compared with the GGG haplotype.[63] Similarly, a polymorphic variant of RET, RET(1476A), was also associated with reduced mRNA synthesis, an almost 10% reduction in kidney volume, and higher levels of the renal function marker cystatin C at birth compared with the RET(1476G) variant in Caucasian newborns.[64] These authors found that newborn kidney volume is proportional to nephron number, therefore PAX2 and RET polymorphisms are likely associated with reduced nephron number in humans.[64] Among 15% of Caucasians inheriting both alleles, newborn kidney sizes were 23% smaller.[65] Surprisingly, however, none of 19 common GDNF gene variants or three single nucleotide polymorphisms related to a putative GDNF-PAX binding site were associated with small kidney size among 163 Caucasians newborns.[65] One rare coding GDNF variant (R93W) was not found in any subject and therefore, the clinical impact of this potential mutation is not known.[65] These early and small studies suggest that genetic polymorphisms in genes that are critical in nephrogenesis may contribute to the wide spectrum of nephron number found in the general population.

Prematurity. Unlike in rodents, postnatal nephrogenesis does not occur in humans, except in extremely premature infants; therefore, nephron number is predominantly determined in utero. Rodriguez et al. examined kidneys from 56 extremely premature infants compared with 10 full-term infants at autopsy.[54] Radial glomerular counts were lower in premature compared with full-term infant kidneys and glomerular number correlated with gestational age, as has been reported previously.[54,66] In addition, they found evidence of active glomerulogenesis (indicated by the presence of basophilic S-shaped bodies under the renal capsule in kidneys) in premature infants up to, but not beyond, 40 days of life.[54] This was the first study to demonstrate ongoing nephrogenesis in humans postnatally. Similarly, in preterm baboons, nephrogenesis was found to continue after birth and nephron number was within the normal range; however, there was a greater proportion of abnormal glomeruli in the superficial cortex compared to full-term controls, suggesting compromised nephrogenesis after premature birth.[67] In contrast, Hinchliffe et al. did not find an increase in nephron number in growth restricted infants who died as stillbirths at varying gestations, or at 1 year of age, suggesting a lack of nephrogenesis after birth.[66,68] Gestational age was found to correlate with nephron number, which reached a maximum around 36 weeks.[69]

Gender. Gender likely plays a complicated role in developmental programming. In the largest series of kidneys analyzed to date, glomerular number in adult females was found to be reduced by up to 12% compared to males.[13,70] In a cohort of Cuban newborns, however, nephron number was not affected by gender.[48] In experimental models, reviewed in detail elsewhere, males generally tend to be more severely affected than females in terms of reduction in nephron number, as well as subsequent manifestation of hypertension and renal dysfunction.[71,72] These differences may in part result from differences in postnatal growth rates between males and females, gender-specific differences in adaptation to adverse events, and gender-specific regulation of genes and pathways impacting renal development, function, and hypertension.[33,72] Similarly, a large study in humans found an association of CKD with low birth weight in adult males, but not in females, suggesting a possible impact of gender on subsequent disease expression, although mechanisms are not yet clear.[73]

Ethnicity. Hoy and colleagues have shown a reduction in nephron number among Aboriginal compared with non-Aboriginal Australians (Table 2.1).[70] Among African Americans and Caucasian Americans, nephron number was not significantly different in both groups and correlated with birth weight, although the distribution appeared to be more bimodal in the African American cohort.[74] No low birth weight subjects were included in this study, but low birth weight is more prevalent among African Americans; therefore, in the general U.S. population, a greater proportion of African Americans may have lower nephron number. This remains to be studied. Nephron number among Senegalese Africans and African Americans was similar.[75] Among Cuban neonates, nephron number was again not different between black compared with white subjects.[48] To our knowledge kidneys of subjects from other ethnic groups have not been studied. Ethnicity, therefore, may have an impact on nephron number, although it is difficult to dissect out an impact independent of its association with birth

weight, socioeconomic factors, genetic polymorphisms, and many other potential confounders.

Intergenerational Factors. Among both white and African American women, mothers who had been of low birth weight had a significantly increased risk of having low birth weight offspring, independent of economic environment, suggesting a cross-generational effect of maternal low birth weight.[76] Similarly maternal, but not paternal birth weights, were associated with offspring birth weight, arguing for an intergenerational programming effect of the maternal environment.[77] Interestingly, in a large population-based study, mothers experiencing preeclampsia, especially when associated with premature birth and low birth weight in the offspring, are at increased risk of subsequent need for renal biopsy and/or ESRD.[47,78] A reduced maternal glomerular filtration rate (GFR) <90 mL per minute and hypertension are significant risk factors for preeclampsia, small for gestational age infants, and premature delivery.[79] The question arises why the mother herself may have been predisposed to these adverse pregnancy-related and renal outcomes. It is conceivable that a vicious cycle may occur where a low birth weight mother would be predisposed to programmed adverse pregnancy outcomes, in turn impacting fetal nephrogenesis and thereby future pregnancy outcomes and renal health of the subsequent generations. To our knowledge this specific association has not been studied in humans. In rats, the first generation offspring of mothers fed low protein diets during gestation had low birth weights, low nephron number, and developed spontaneous hypertension at 8 weeks of age. Offspring of these first generation females, although maintained on normal diets throughout gestation, also exhibited low nephron number and hypertension, demonstrating intergenerational programming.[80] Interestingly the effect was lost by the third generation, suggesting that the intergenerational cycle can be interrupted by optimization of risk factors such as maternal nutrition.

Strategies for Augmentation of Nephron Number

Although total filtration surface area in individuals with fewer nephrons may not be reduced, as a result of compensatory hypertrophy of the existing nephrons (see later), low nephron number is still associated with an increased risk of hypertension and renal dysfunction in later life. Strategies to optimize nephron number may therefore have an important impact on clinical disease (Table 2.2). Interventions would likely need to be applied during gestation to have an optimal effect. Ideally, optimization of all modifiable risk factors prior to pregnancy would appear the simplest and most widely applicable intervention. Clinically feasible interventions are being studied to potentially "rescue" nephron number and reduce subsequent hypertension.

Postnatal Nutrition

Provision of adequate postnatal nutrition in low birth weight rat pups, achieved by cross-fostering onto normal lactating females at birth, led to restoration of nephron number and prevented the development of subsequent hypertension compared to pups with continued growth restriction.[81]

Vitamin A Supplementation

Because vitamin A deficiency is associated with a nephron deficit, administration of a single dose of retinoic acid during early nephrogenesis restored nephron number to control levels in rat pups exposed to low protein diet in utero.[82] Postnatal administration of retinoic acid to preterm baboons, however, was not able to stimulate nephrogenesis compared to preterm controls, suggesting a more proximal window for the effect of vitamin A on nephrogenesis, although these results may have been confounded by routine antibiotics given to all animals, which may have negatively impacted nephrogenesis, confounding a potentially small vitamin A effect.[30]

Genetics

In a cohort of Caucasian newborns, a common variant of the ALHD1A2 gene involved in retinoic acid metabolism, ALHD1A2rs7169289(G), was associated with a 22% increase in newborn kidney size, and higher cord blood retinoic acid levels, compared to the wild-type ALDH1A2 rs7169289(A) allele.[83] These authors suggest this gene polymorphism could be protective for nephrogenesis in the setting of vitamin A deficiency.

Prevention of Low Nephron Number

The ubiquitous plasma membrane protein Na^+/K^+-ATPase functions as an ion pump as well as a signal transducer. Ouabain is a highly specific Na^+/K^+-ATPase ligand that triggers the release of calcium waves, which are important regulators of early development.[84] Interestingly, erythrocyte membrane Na^+/K^+-ATPase activity was found to be reduced in a cohort of low birth weight males at age 20, making this a potentially relevant pathway.[85] The impact of ouabain administration was studied experimentally as a modulator of nephrogenesis under protein-deficient conditions in vitro and in vivo.[86] Ouabain was found to abrogate the effect of serum starvation on ureteric bud branching in cultured metanephroi, and to prevent reduction in nephron number in offspring of low protein diet-fed dams.[84] The ouabain was administered throughout pregnancy in this study and, therefore, the potential of ouabain to rescue or restore nephron number once an adverse event is already established has not been studied. Similarly, supplementation of maternal diet during gestation with glycine, urea, or alanine prevented the reduction in nephron number induced by maternal low protein diet in all offspring, but blood pressure was only normalized in those receiving glycine.[24] Interestingly, nephron number in the offspring of mothers subjected to water restriction during gestation was increased, but also did not abrogate development of subsequent hypertension—again suggesting possible divergent programming mechanisms for nephron number and blood pressure in some models.[87]

Maternal Nephrectomy

Uninephrectomy in rat mothers prior to pregnancy has been associated with an increase in offspring nephron number at birth; however, at 6 weeks, nephron numbers were not different from offspring of nonnephrectomized dams.[88,89] These authors suggest a possible circulating renotrophic factor in response to maternal uninephrectomy, possibly inducing hypertrophy of the contralateral kidney, which may accelerate nephrogenesis in the fetus but may not affect ultimate nephron number. These observations may be relevant in human cases such as maternal renal transplantation or maternal kidney donation, although timing of pregnancy in relation to nephrectomy may be an important variable. This area deserves more investigation.

CLINICAL SURROGATES FOR NEPHRON NUMBER

In vivo, nephron number can only be grossly estimated by MRI or kidney biopsy.[18,70,90] Associations of nephron number with readily available clinical variables have been described and are outlined in Table 2.3.

Anthropomorphic Features

Birth Weight

Low birth weight is defined by the World Health Organization as a birth weight under 2,500 g. Very low birth weight is usually defined a below 1,500 g. Low birth weight could result from prematurity itself (i.e., birth before the 37th week of gestation with an appropriate weight for gestational age), or from intrauterine growth restriction (IUGR) at any gestation.[46] A small for gestational age infant is defined as having a birth weight below the 10th percentile of normal for that gestational age.[46] Full-term IUGR is the most strongly associated with adult disease.[91] Risk factors for low birth weight are diverse and, in poorer countries, maternal malnutrition, poor prenatal care, and infections are common, whereas in the developed world, factors such as high risk pregnancies, assisted reproduction, multiple gestations, and advanced maternal age are becoming more frequent.[46,92] High birth weight is defined variably as a birth weight >4,000 g or >4,500 g, and is associated with maternal obesity, maternal diabetes, prolonged gestation, and reduced maternal smoking.[93] High birth weight has also been associated with adverse renal outcomes in the offspring, especially as a consequence of maternal diabetes.[94,95]

2.3 Clinical Surrogates for Low Nephron Number

Clinical Feature	Association with Nephron Number	Population	Reference
Low birth weight	↑ of 257,426 glomeruli per kg increase in birth weight	U.S. white and black, children and adults	19
Prematurity	↓ glomerular number in premature compared to term infants	U.S. premature and full term neonates	54, 68
Gender	Nephron number is 12% lower in females	U.S. white and black Aboriginal Australian	70
Age	↓ 3,676 glomeruli per kidney per year of age >18 years	U.S. white and black Aboriginal Australian	70
Adult height	↑ 28,000 glomeruli per centimeter increase in height	Australian Aboriginal German, white	10, 70
Kidney mass	↑ 23,459 glomeruli per gram of kidney tissue	Infants <3 months of age	64
Glomerular volume	Inverse correlation between glomerular volume and nephron number	U.S. white and black Aboriginal Australian German adults, Cuban infants	10, 13, 48
Ethnicity	↓ Aboriginal Australians compared to U.S. white and black	U.S. white and black Aboriginal Australian	70

↑, increase; ↓, decrease.

Low birth weight is the strongest current clinical surrogate for nephron number. Nephron number has consistently been shown to correlate strongly with birth weight in humans, with an extrapolated increase of 257,426 glomeruli per kilogram increase in birth weight.[19,48,54,70] The relationship of birth weight to nephron number is preserved among Australian Aboriginals, African Americans, and Whites and therefore may be generalizable to other populations.[19,70] The specific relationship between nephron number and low birth weight has only been examined in infants. Low birth weight was associated with lower nephron number than normal birth weight, and was similar among black and white subjects.[48,68] In experimental animals, however, not all low birth weight animals have been found to have reduced nephron number and, conversely, low nephron number has been reported in the absence of low birth weight.[96,97] Birth weight alone, therefore, is not a universal surrogate for nephron number. To our knowledge, nephron number has not been specifically studied in high birth weight humans or animals. Other anthropomorphic correlates that have been associated with nephron number are highlighted in Table 2.3.[18,20,70,98]

Kidney Size

Renal Mass

From autopsy studies, nephron number has been found to correlate directly with kidney weight in both adult and infant cohorts.[18,64] Zhang et al. calculated a predicted increase of 23,459 glomeruli per gram of kidney mass in infants under 3 months of age.[64] In living subjects, kidney weight is not routinely obtainable, but donor kidney mass measured prior to transplantation, as a measure of nephron "dose," has been shown to have clinical relevance (see later).

Kidney Volume

Kidney volume can be measured in vivo, making it an attractive potential surrogate for nephron number. Renal volume is dependent on nephron number, but is also strongly

2.4 Differences in Nephron Number, Glomerular Volume, and Total Glomerular Surface Area in the Right Kidney, U.S./Australian Adults (18+ years), Means (SD)

		All	No hypertension	Hypertension	No Hypertension versus Hypertension
US whites	Nglom	855 183 (295 247)	894 339 (275 956)	747 727 (271 155)	P = 0.026
	Nglom adj[a]	866 722 (289 896)	912 876 (283 744)	779 808 (288 510)	P = 0.046
US blacks	Nglom	921 708 (318 089)	931 463 (290 529)	912 480 (350 329)	P = 0.776
	Nglom adj[a]	946 379 (322 516)	949 934 (288 768)	952 441 (353 197)	P = 0.97
Aborigines	Nglom	733 484 (217 763)	843 423 (199 384)	631 321 (105 298)	P = 0.04
	Nglom adj[a]	776 422 (253 631)	912 539 (218 432)	653 241 (178 609)	P = 0.110
US whites	Mean Vglom, gmean	7.1 (6.6–7.6)	6.87 (6.3–7.5)	7.82 (6.9–8.9)	P = 0.096
US blacks	Mean Vglom, gmean	7.7 (7.2–8.3)	6.92 (6.3–7.6)	8.64 (7.8–9.5)	P = 0.0012
Aborigines	Mean Vglom, gmean	7.7 (6.5–9.0)	6.88 (5.4–8.7)	8.0 (5.3–11.9)	P = 0.426
US whites	Vglomtot, cm^3	5.68 (5.3–6.1)	5.79 (5.2–6.5)	5.34 (4.7–6.3)	P = 0.484
US blacks	Vglomtot, cm^3	6.74 (6.3–7.3)	6.16 (5.6–6.8)	7.34 (6.6–8.2)	P = 0.020
Aborigines	Vglomtot, cm^3	5.40 (4.6–6.3)	5.89 (4.4–7.4)	4.96 (3.9–6.3)	P = 0.365

Nglom, Nglom adj, and Vglomtot: arithmetic means (SD). Vglomtot is the combined volume of all glomeruli in the kidney. Vglom in $\mu m^3 \times 10^6$, geometric mean (95% confidence interval). Nglom for US whites versus US blacks, P = 0.133. Nglom adj for US whites versus US blacks, P = 0.079. Nglom for Aboriginal versus other, P = 0.047.

[a]Nglom adj: adjusted for proportions of sclerosed glomeruli seen on light microscopy.

Reprinted with permission from Hoy WE, Bertram JF, Denton RD, et al. Nephron number, glomerular volume, renal disease and hypertension. Curr Opin Nephrol Hypertens. 2008;17:258–265.

correlated with current body size.[18] In fetuses and at birth, kidney volume is presumed to be directly proportional to nephron number; however, once normal kidney growth and adaptation occurs after a few months of life, impacted by body surface area, age, gender, glomerular hypertrophy, or nephron loss through injury, the relationship likely becomes less linear.[63] Despite this caveat, several authors have investigated utility of renal volume in relation to birth weight. Evaluation of fetal renal function by ultrasound in growth restricted fetuses in utero found reduced hourly urine output, greater oligohydramnios, reduced renal perfusion, and smaller kidney volume compared to normally growing fetuses.[99–101] Although these findings could simply reflect globally reduced renal perfusion, abnormal renal development cannot be excluded. Another study utilizing serial ultrasounds in a cohort of small for gestational age compared to appropriate for gestational age fetuses found that kidneys were smaller in the small for gestational age cohort, although kidney length was relatively preserved compared to width and circumference after 26 weeks of gestation.[102] Follow-up of kidney size and growth postnatally in 178 premature or small for gestational age children, compared with 717 term appropriate for gestational age controls, at 0, 3, and 18 months found that weight for gestational age correlated with kidney volume at all three time points.[103] Slight catch-up in kidney growth was observed in the growth-restricted, but not the premature infants. Among a cohort of low birth weight Australian Aboriginal children aged 5 to 18, renal volumes were found to be lower when adjusted for body size compared to normal birth weight children.[104] These authors also found that the reduction in kidney volume was driven more by a shorter depth than length of the kidney. Kidney length and volume were also both found to be smaller in a cohort of low birth weight children aged 10 to 12 years, and correlated weakly with lower GFR (Fig. 2.2).[105] In contrast, others found no difference in kidney volume, adjusted for body surface area and gender, between individuals who had been appropriate weight for gestational age at term, small for gestational age at term, or preterm at age 9 to 12 years.[106] Among young adults born premature (either appropriate or small for gestational age) compared with term age-matched controls, prematurity was associated with smaller kidneys at age 20 years, whereas IUGR had only a small, nonsignificant effect.[107] Kidney volume may therefore be less reliable as a surrogate for nephron endowment as subjects age. In addition, as a note of caution, renal volumes were not comparable between ultrasound and MRI in a neonatal population, suggesting that the same imaging modality should be used if measurements are to be compared.[108]

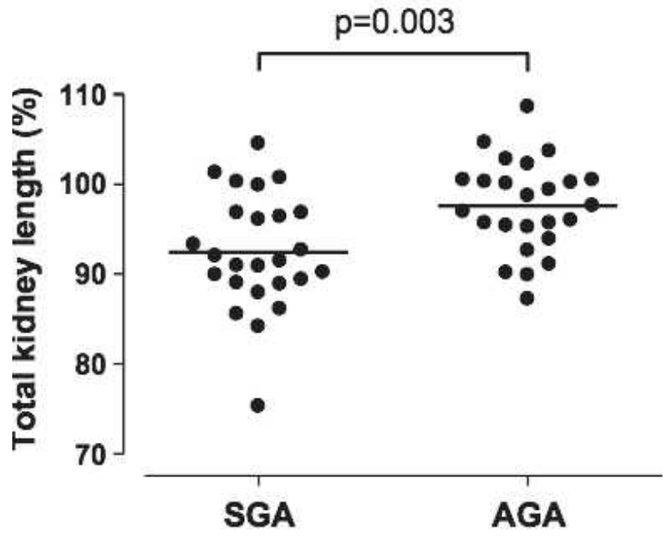

FIGURE 2.2 Correlation between growth restriction and kidney length. Kidney length (expressed as percent expected from the literature) is significantly shorter in Caucasian children aged 11.3 ± 2.1 years who were born small weight for gestational age (SGA) compared with appropriate weight for gestational age (AGA) at birth. (Reprinted with permission from Simonetti GD, Raio L, Surbek D, et al. Salt sensitivity of children with low birth weight. *Hypertension*. 2008;52:625–630.)

Histologic Features

Glomerular Volume

Glomerular number has been found to vary up to 13-fold among all the cohorts studied, and glomerular volume has been found to vary up to 6.7-fold (Table 2.1).[13] Because nephron number is fixed at birth, glomerular size is likely the major variable determining adaptation of filtration capacity to match the body's demands.[19,20,48,98,109,110] Indeed, calculated total filtration surface area in kidneys with varying nephron number tends to be very similar, suggesting compensatory hypertrophy in those with fewer nephrons as shown in Table 2.4.[9] Consistent with this, mean glomerular volumes vary directly with body size, and inversely with nephron number and birth weight in all populations studied (Fig. 2.3).[10,48,70,111] Most studies, however, report mean glomerular volumes for a whole kidney. Further investigation into glomerular heterogeneity has found significant inter- and intraindividual variability in glomerular size.[13,112] Individual glomerular volume was found to vary up to eightfold within a single subject.[13] Glomerular size tended to be larger and more variable in the outer cortex compared to those deeper within the kidney.[13] In multiple analyses, hypertension, obesity, age, and low nephron number emerged as major predictors of larger glomeruli and greater heterogeneity.[13,70,75,111–113] Interestingly, consistently, African American and African subjects have higher mean glomerular volumes and greater heterogeneity of glomerular volume compared to white subjects, independent of nephron number (Fig. 2.4).[13,75] Furthermore, between Senegalese and African American subjects, glomerular volumes were higher in the U.S. cohort after controlling for body size.[75] Increased glomerular volume and heterogeneity therefore may result from different mechanisms among African origin populations compared to Caucasians. Whether this may have posed an evolutionary survival advantage which may be maladaptive in the current environmental circumstances given the greater burden of renal disease among African Americans, or whether this may reflect differences in glomerular perfusion, circulating glucose concentrations, or chronic inflammation, remains to be elucidated.[75,114] It is possible that the

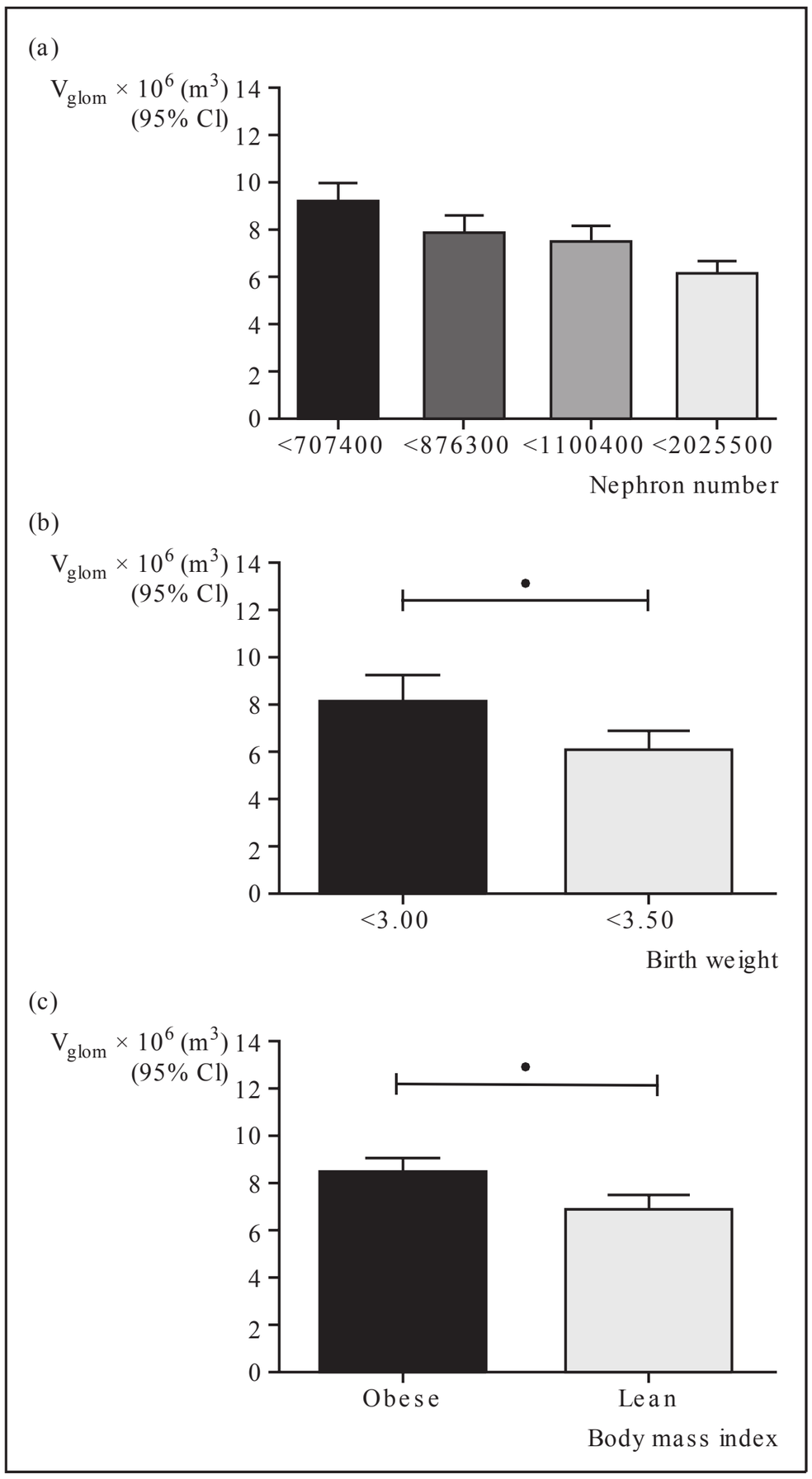

FIGURE 2.3 Relationship of glomerular volume (V_{glom}) to nephron number, birth weight, and body size. **A:** Inverse association of mean glomerular volume (V_{glom}) with nephron number, $n = 252$; **(B)** inverse association of mean glomerular volume (V_{glom}) with birth weight, $n = 58$; and **(C)** direct association of mean glomerular volume (V_{glom}) with body mass index (BMI; obese $\geq$30 kg per m^2, $n = 95$; lean $<$25 kg per m^2, $n = 78$). Subjects were U.S. whites and African Americans. * $P < 0.05$. (Reprinted with permission from Puelles VG, Hoy WE, Hughson MD, et al. Glomerular number and size variability and risk for kidney disease. *Curr Opin Nephrol Hypertens.* 2011;20:7–15.)

greater average adult height among African American subjects may augment final nephron number, diminishing the relationship with birth weight, but may not compensate for, or may exacerbate, other potentially programmed changes such as glomerular size. Compensatory hyperfiltration may be adequate in the short term to augment glomerular filtration, but sustained hyperfiltration, especially in the setting of additional renal stresses (e.g., rapid growth, hypertension, diabetes) will eventually become maladaptive and contribute to ongoing nephron loss. A kidney starting with fewer nephrons would therefore reach a critical deficit within a shorter time. Consistent with this, evaluation of glomerular size in donor kidney biopsies again found higher maximal planar area of glomeruli to be a predictor of poorer transplant function and, again, glomerular size was higher in African American subjects.[115] From a clinical point of view, therefore, an otherwise unexplained increased in glomerular volume should raise the suspicion of a coexisting reduction in nephron number, although this relationship is less clear in African origin populations.

Pathologic Changes

Most renal biopsy results in subjects with lower nephron number have commented on glomerular size. In general the degree of glomerulosclerosis present in kidneys with low nephron number has been found to increase with age and hypertension, but has not been a prominent feature in most studies.[116] The pattern of glomerulosclerosis has been described as a global ischemic collapse rather than classical focal and segmental glomerulosclerosis that might have been expected with hyperfiltration causing cumulative glomerular injury.[74] A recent case series of six very low birth weight subjects, aged 15 to 52 years, who had been born prematurely, however, did find evidence of secondary focal and segmental glomerulosclerosis, associated with glomerulomegaly in all biopsies.[117] Although all biopsies were performed because of a clinical indication, and therefore may not be a generalizable sample, the authors suggest that low birth weight was a common denominator predisposing to hyperfiltration and glomerulosclerosis. Analyses of histologic changes in human biopsies may be confounded by multiple factors. In kidneys of rats exposed to gestational low protein diet, fewer and more immature glomeruli were present on day 10 at the end of nephrogenesis, exhibiting a markedly thickened glomerular basement membrane and abnormal podocyte structure (Fig. 2.1).[118] Similarly, in prehypertensive Gdnf heterozygous mice, which have a 30% reduction in nephron number, glomerular enlargement was observed, associated with an increase in cellular proliferation, thickened glomerular basement membrane, reduced podocyte density, and a mild expansion of the tubulointerstitium.[119] In rats rendered diabetic at 12 weeks, and followed until 40 weeks, glomerular changes associated with diabetes were similar in those that had been of low birth weight compared to normal birth weight. However, again, in addition to lower nephron number, podocyte density was reduced and the area covered by each podocyte was greater in the low birth weight diabetic animals.[120] Interestingly, proteinuria tended to be higher in the low birth weight group, likely suggesting a greater degree of hyperfiltration. Taken together, these authors postulate that early subtle structural abnormalities in kidneys with reduced nephron number may enhance susceptibility to subsequent renal injury.

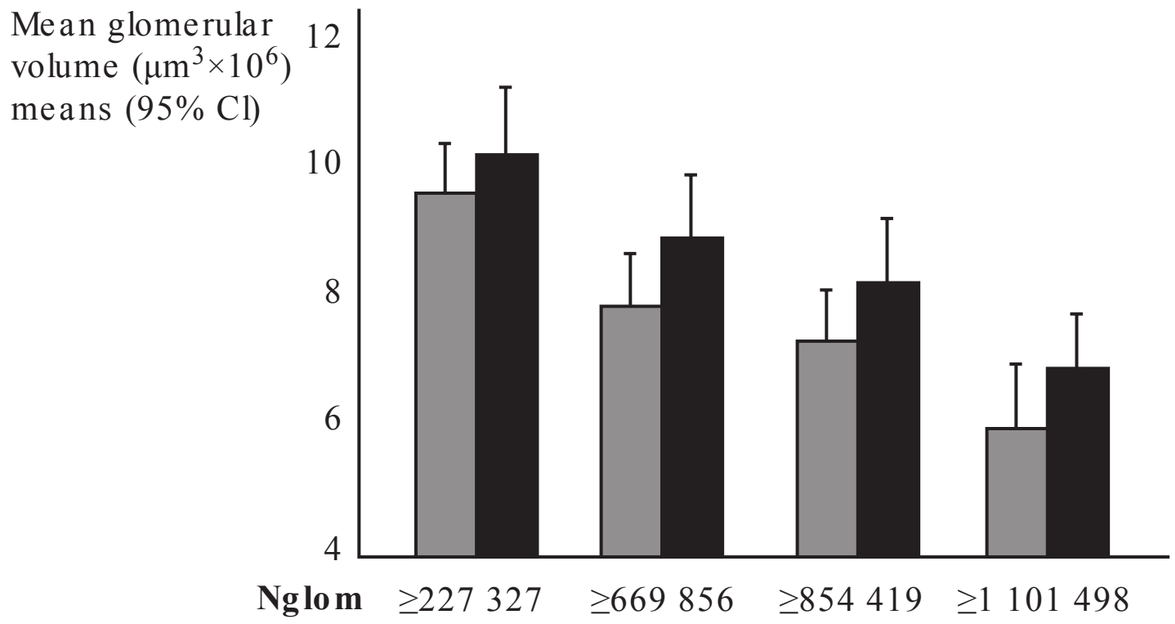

FIGURE 2.4 Relationship between mean glomerular volume and glomerular number (Nglom) in U.S. whites and African Americans. Mean glomerular volume by quartiles of glomerular number. *Light bars* are U.S. whites and *dark bars* are African American adults. U.S. whites, P for trend <0.0001; African Americans *P* for trend $= 0.0008$. (Reprinted with permission from Hoy WE, Bertram JF, Denton RD, et al. Nephron number, glomerular volume, renal disease and hypertension. *Curr Opin Nephrol Hypertens*. 2008;17:258–265.)

CLINICAL IMPACT OF NEPRHON MASS

Blood Pressure

Birth Weight and Blood Pressure

Many studies in humans and animal models have supported the observation that low birth weight is associated with higher blood pressures in later life (Fig. 2.5).[12,121–127] Higher blood pressures have been reported in newborns of lower birth weight, therefore this programming effect is evident early and tracks through to adulthood (Fig. 2.6).[127] Importantly, low birth weight children tend to have higher blood pressures, although not in the hypertensive range, compared to normal birth weight children. With increasing age, however, blood pressure differences between low birth weight and normal birth weight subjects become amplified and do reach hypertensive levels with time.[128,129] Prematurity and gestational age have also been associated with higher blood pressures in young adults; however, low birth weight for gestational age was a more significant predictor of blood pressure at birth and 18 years of age than low birth weight of prematurity.[107,130–133] This observation suggests that ongoing intrauterine stress may have a greater impact than premature birth. Consistent with this possibility, abnormal placental morphology, a marker of adverse intrauterine conditions, has been associated with higher blood pressures in children at 7 years of age.[134] The importance of the intrauterine environment has also been highlighted in both monozygotic and dizygotic twin studies, where the lower birth weight twin has been found to have a greater increase in blood pressure in infancy and higher blood pressure in adulthood.[135,136] These data have been interpreted to suggest that genetic factors play a smaller role than fetal growth in developmental programming. Although this may be the case, a significant modulation of the relationship between birth weight and blood pressure has been found by genotype of beta adrenergic receptors, suggesting possible developmental interaction with gene expression as well.[137] The relationship between birth weight and blood pressure has not been universally found, however, and in particular appears to be weaker, but not always absent, in African American children.[128,138–142] However, interestingly, the association between low birth weight and higher blood pressures does appear preserved in African and Caribbean black children, suggesting that early childhood growth rates, genetic, and/or other environmental factors are also important.[143–145] Current body mass index (BMI) is a frequent confounder in these studies, and may play a greater role among black compared to white subjects.[137]

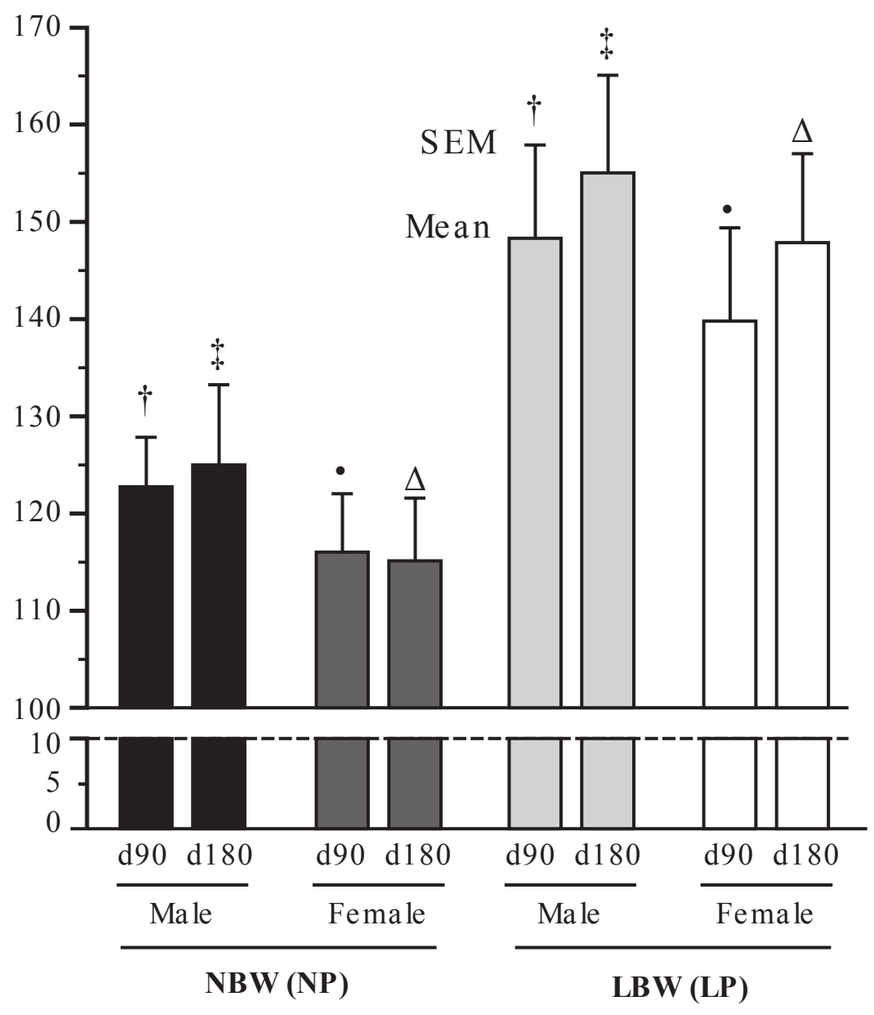

FIGURE 2.5 Relationship between birth weight, nephron number, and hypertension in rats subjected to maternal normal (NP) or low (LP) protein diet. Systolic blood pressure in 90-day-old (d90) and 180-day-old (d180) male and female rats with normal (NBW) or low (LBW) birth weights. Symbols indicate group comparisons, $P<0.05$. (Reprinted with permission from Villar-Martini VC, Carvalho JJ, Neves MF, et al. Hypertension and kidney alterations in rat offspring from low protein pregnancies. *J Hypertens Suppl*. 2009;27:S47–51.)

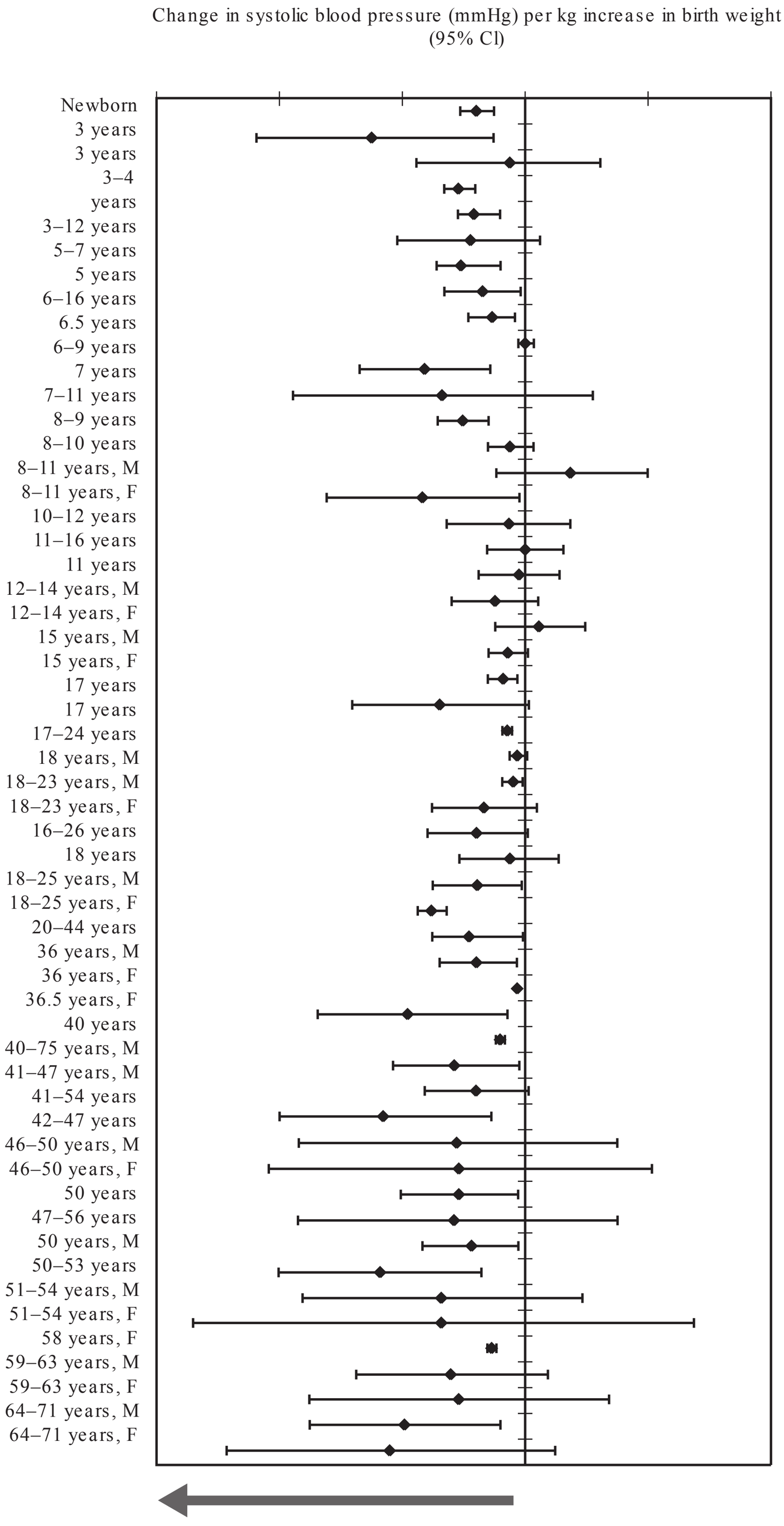

FIGURE 2.6 Studies reporting multiple regression analyses in children, adolescents, and adults. Higher blood pressures are generally associated with lower birth weights across all ages and in both genders. *CI*, confidence interval. See original source for detailed references. (Reprinted with permission from Huxley RR, Shiell AW, Law CM. The role of size at birth and postnatal catch-up growth in determining systolic blood pressure: a systematic review of the literature. *J Hypertens*. 2000;18:815–831.)

Nephron Number and Blood Pressure

The association between low birth weight and later life hypertension has been well documented in various animal models utilizing gestational interventions such as maternal dietary protein restriction, dexamethasone administration, or uterine artery ligation, as described previously.[12,28,37,146–150] The link between low birth weight and subsequent spontaneous hypertension in these models appears to be, at least in part, attributable to an inborn nephron deficit.[12,37,148] Most interventions result in a 20% to 30% reduction in glomerular number in offspring, and hypertension emerges by early adulthood.[12,151] Conversely, optimization of postnatal nutrition after growth restriction has been found to normalize nephron number and abrogate the development of hypertension in rats, suggesting that nephron number per se is an important contributor to the pathogenesis of hypertension.[24,81,152] In contrast, however, augmentation of nephron number does not always protect against high blood pressure. Restoration of nephron number by supplementation of maternal low protein diet with glycine, urea, or alanine only normalized blood pressure in the offspring supplemented with glycine.[24] Similarly, a 20% increase in nephron number, induced by postnatal overfeeding in normal birth weight rats, did not prevent hypertension and glomerulosclerosis with age, although concomitant obesity may have been a confounder in this study.[152] Based on these studies, therefore, developmental programming of hypertension is dependent on more than a reduction in nephron number, although under certain circumstances nephron number does appear to be the predominant predisposing factor.

Evidence in humans suggests a similar association between nephron number and risk of hypertension. In a cohort 35- to 59-year-old European Caucasians who died in accidents, mean nephron number was significantly lower, and glomerular volume significantly higher in the 10 subjects with a history of essential hypertension, compared to 10 normotensive matched controls.[10] There was no evidence of disproportionate glomerulosclerosis or renal injury, leading the authors to suggest that an intrinsic deficit in nephron number was the most likely factor associated with development of essential hypertension. Birth weights were not available in this study, therefore potential associations with nephron number could not be speculated. A possible limitation of this study is the high mean glomerular number in the nonhypertensive group compared to that reported in other Caucasian populations; however, mean nephron number in the hypertensive group was similar to that in a hypertensive U.S. Caucasian cohort. Similarly, lower nephron numbers have been associated with higher blood pressures among Caucasians and Australian Aboriginal subjects, although the relationship is not as consistent among subjects of African origin (Fig. 2.7).[10,70,98] Conversely, the prevalence of hypertension was found to be lower among Caucasians and Australian Aboriginals with higher nephron numbers, suggesting a protective effect of higher nephron numbers in these populations.[70,113] An important caveat is that these studies are all performed on postmortem kidney samples mostly from adults of varying ages, and therefore may not reflect nephron endowment at birth. Much larger sample sizes would be required to control for all possible confounding variables between subjects, which are not easily feasible. In addition, associations have been well described between birth weight and nephron number, nephron number and hypertension, and birth weight and hypertension but, to date, to our knowledge, no study has analyzed nephron number, birth weight, and hypertension in individual subjects.

Timing of nephron loss appears to impact subsequent risk of hypertension and renal disease. In humans, congenital conditions associated with significant reductions in nephron mass (e.g. unilateral renal agenesis or bilateral renal hypoplasia) result in worsening proteinuria, hypertension, and renal dysfunction with time.[11] In contrast, nephrectomy later in life, resulting in a comparable loss of nephron mass, does not necessarily result in progressive renal functional decline.[153] Similarly, nephrectomy in adult animals in varying experimental settings does not invariably lead to hypertension and renal dysfunction.[154] Removal of a kidney on postnatal day 1 in rats, or fetal uninephrectomy in sheep (i.e., loss of nephrons during active nephrogenesis), however, does lead to adult hypertension in the absence of evidence of renal injury.[155–157] Taken together these animal and human observations suggest that loss of nephrons during renal development, as opposed to after nephrogenesis is completed, may have a more critical impact on the long-term risk of hypertension.

In support of this hypothesis, glomerular numbers in adult rats were similar after uninephrectomy at day 3 or day 120 of age; however, a greater proportion of immature glomeruli were present in kidneys of rats having undergone removal of the contralateral kidney at day 3.[158] In addition, mean glomerular volume compared to controls was 59% higher in rats undergoing neonatal nephrectomy compared with 20% higher in rats nephrectomized as adults, suggesting more vigorous compensatory hypertrophy and hyperfunction in response to neonatal nephrectomy, which may become maladaptive over the long term. Developmentally acquired low nephron mass may, therefore, be considered along the broader continuum of renal hypoplasia and associated with long-term consequences.[13]

Glomerular Volume and Blood Pressure

Glomerular volume varies inversely with nephron number and, in U.S. White, Black, and Australian Aboriginal subjects, is associated with increased risk for high blood pressure (Fig. 2.8).[70] In addition, among the U.S. Black and Australian Aboriginal populations, large glomeruli on renal biopsy are associated with poorer renal outcomes in native and transplanted kidneys.[98,115,159,160] Among Black subjects, glomerular size appears to be an independent predictor of higher blood pressure, whereas in White and Australian Aboriginal subjects, the relationship appears also dependent on low nephron number.[113]

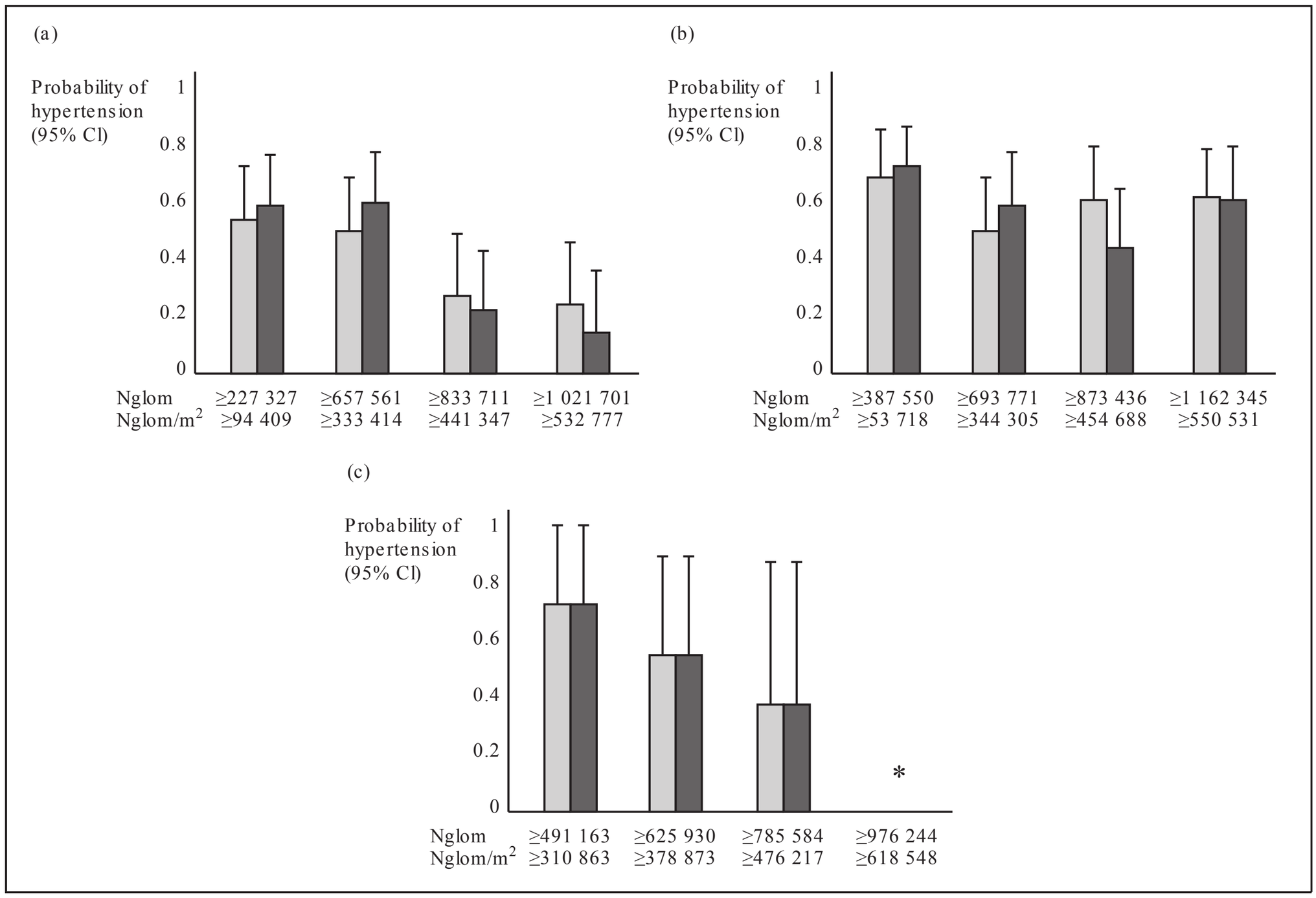

FIGURE 2.7 Probability of hypertension by glomerular number (Nglom) and ethnicity. Probability of hypertension in **(A)** U.S. white adults, by Nglom (*light bars*), $P = .097$; adjusted for sex, $P = .042$. By Nglom per m^2 body surface area (BAS), Nglom per m^2 (*dark bars*), $P = .0012$; adjusted for sex, $P = .0006$. **B:** African American adults, by Nglom, $P = .625$; adjusted for sex, $P = .71$. By Nglom per m^2, $P = .246$; adjusted for sex, $P = .245$. **C:** Australian Aboriginal adults, by Nglom, $P = .167$; adjusted for sex, $P = .173$. By Nglom per m^2, $P = .167$; adjusted for sex, $P = .109$. *Among subjects with Nglom in this category none had hypertension. *CI*, confidence interval. (Reprinted with permission from Hoy WE, Bertram JF, Denton RD, et al. Nephron number, glomerular volume, renal disease and hypertension. *Curr Opin Nephrol Hypertens*. 2008;17:258–265.)

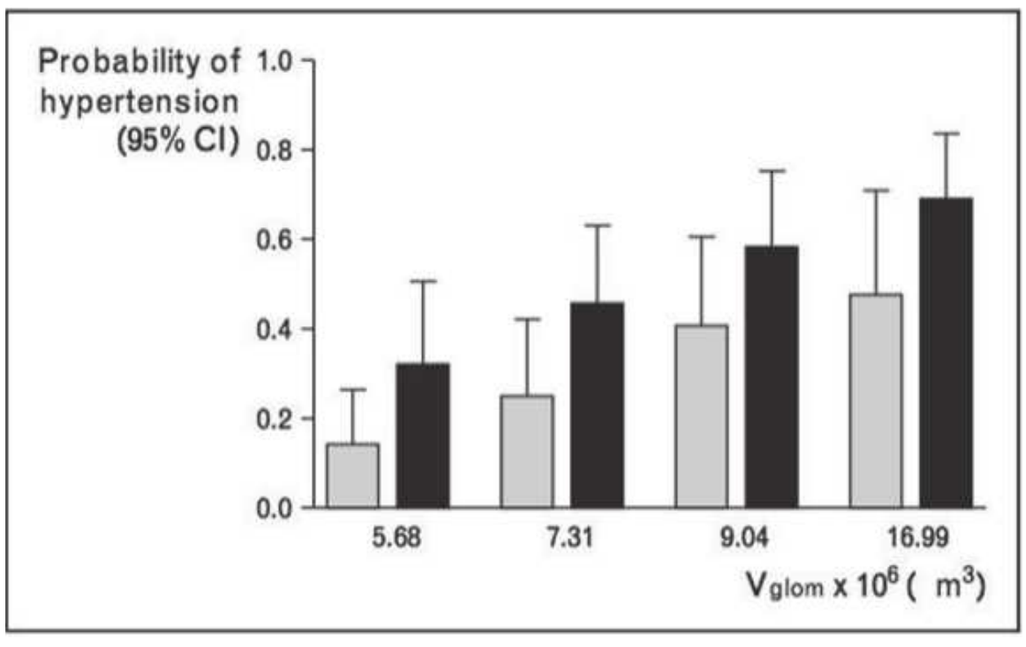

FIGURE 2.8 Probability of hypertension by glomerular volume (V_{glom}) in U.S. white and African American adults. Increasing probability of hypertension with increasing (V_{glom}) in U.S. white (*light bars*) and African American (*dark bars*) subjects aged 18 years or older ($n = 252$). (Reprinted with permission from Puelles VG, Hoy WE, Hughson MD, et al. Glomerular number and size variability and risk for kidney disease. *Curr Opin Nephrol Hypertens*. 2011;20:7–15.)

The observation that in some animal models normalization of nephron number did not prevent development of subsequent hypertension, argues against nephron number being the sole programmed link between early developmental stress and higher blood pressures.[161,162] Given that the filtration surface area in kidneys with low nephron numbers has not been found to be significantly lower than in kidneys with a higher number of nephrons, and may even be increased in subjects with hypertension (Table 2.4), other nonglomerular contributors to sodium avidity in low birth weight kidneys have been investigated.[8,10,70] Blood pressure is dependent on renal, neuroendocrine, and vascular factors, all of which may be subject to simultaneous developmental programming.[8] Programmable vascular factors which have been studied include altered structure and function of large vessels, impaired vascular reactivity, and endothelial dysfunction, which are reviewed in detail elsewhere.[163–165] Neuroendocrine factors include altered stress responsiveness, cortisol levels, insulin resistance, and sympathetic nervous system activity.[71,166,167] Within the kidney, in addition to programming of nephron

number, alterations in sodium transport and modulation of the renin-angiotensin system have also been well described.

Renal Programming of Blood Pressure

Salt Sensitivity and Birth Weight

The original programming hypothesis postulated a reduction in filtration surface area and limitation in sodium excretory capacity in a kidney with fewer nephrons.[2] Consistent with this, prenatal dexamethasone administration in rats was associated with lower GFR, higher urine albumin excretion, reduced urinary sodium excretion, and higher tissue sodium content compared to controls.[37] Interestingly, in a study of Caucasian men aged 20 years, those who had been of low birth weight had an increase in systolic blood pressure and no change in GFR, but an increase in fractional excretion of sodium compared to normal birth weight controls.[85]

Salt-sensitive hypertension has subsequently been shown in low birth weight rats (induced by uterine artery ligation), and in adult rats that had been exposed to maternal gestational diabetes.[52,168,169] In contrast, however, blood pressures did not increase more in low birth weight rats (induced by maternal protein restriction) compared to normal birth weight rats on a high salt diet.[170] Timing of the dietary sodium challenge may have an impact, however.[171] Blood pressure rises more consistently in response to a high salt diet in older rats, suggesting loss of potential adaptive mechanism with age, or greater susceptibility to salt sensitivity as nephron numbers decline with age.[172] Plasma volume and blood pressures were found to be higher in low birth weight compared to normal birth weight juvenile rats on normal diets, however, suggesting positive sodium balance at baseline.[173] Interestingly, although a further increase in sodium intake did not increase blood pressures or plasma volume expansion more than in normal birth weight rats, GFR was significantly increased in the low birth weight rats on a high sodium diet, suggesting a shift in the pressure natriuresis curve.[173] These rats were subjected to global malnutrition in utero, therefore a low sodium diet during gestation, which also may have modulated their renal sodium handling. Interestingly, manipulation of sodium intake postnatally was found to impact long-term blood pressure in young low birth weight rats.[174] Low birth weight rats were placed on either low, normal, or high salt diets from weaning to 6 weeks of age, followed by normal diets thereafter. Later life hypertension was abrogated by early low salt diet and worsened by early high salt diet. In addition, salt sensitivity after 40 weeks was lost in the rats subjected to early low salt diets.[174] Early low salt diet therefore appears to be able to "re-program" the kidney and prevent hypertension in low birth weight rats.

Filtration surface area, blood pressure, and response to sodium loading was assessed in GNDF heterozygous mice in which nephron numbers are reduced, and 20% of animals have unilateral renal agenesis.[175] Total nephron number was reduced by 25% in mice with two kidneys (HET2K) and 65% in mice with single kidneys (HET1K) compared to the wild type. The degree of glomerular hypertrophy was similar in HET1K and HET2K, resulting in normalization of glomerular surface area in HET2K but a persistent reduction in the HET1K. In this model, reduced nephron number alone was not associated with increased blood pressures, but both groups of HET mice became significantly hypertensive on a high sodium diet, with blood pressures being highest in the HET1K mice.[175] Interestingly, at baseline urine sodium excretion was progressively higher in HET2K and HET1K mice, suggesting augmented natriuresis that maintained normal blood pressures. In the same model, tubule sodium transporters were not found to be increased, in contrast to other programming models. This suggested a different adaptation in baseline sodium handling in this genetic model, which may be overwhelmed in the face of a high sodium diet.[119,175]

In healthy human adults, salt sensitivity was found to correlate inversely with birth weight, independent of GFR (Fig. 2.9).[176] Similarly, in low birth weight children, the prevalence of salt sensitivity was found to be high and to correlate

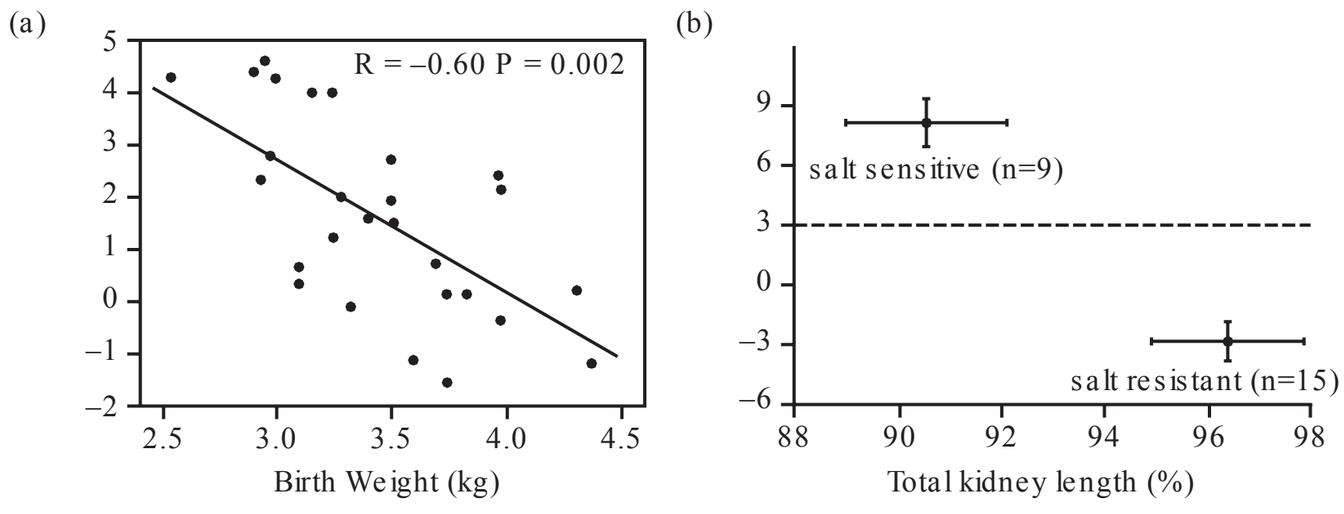

FIGURE 2.9 Salt-sensitivity in humans relative to birth weight and kidney length. **A:** Correlation between birth weight and salt sensitivity in 27 normotensive subjects aged 37.2 ± 14.5 years. **B:** Correlation between salt sensitivity and percent expected kidney length in children aged 11.3 ± 2.1 years. Kidney lengths were smaller in children who had been small weight for gestational age (SGA) compared to appropriate weight for gestational age (AGA) children at birth, suggesting a correlation of salt sensitivity with birth weight. (**A**, reprinted with permission from de Boer MP, Ijzerman RG, de Jongh RT, et al. Birth weight relates to salt sensitivity of blood pressure in healthy adults. Hypertension 2008;51:928–932. **B**, reprinted with permission from Simonetti GD, Raio L, Surbek D, et al. Salt sensitivity of children with low birth weight. *Hypertension*. 2008;52:625–630.)

inversely with kidney size, again independent of GFR, suggesting that renal function itself was not a confounder (Fig. 2.9).[105] Developmental programming of blood pressure in most animal models and humans does, therefore, appear to be associated with altered sodium handling by the kidney.

Renal Sodium Transport

The expression of renal sodium transporters has been investigated in several animal models of developmental programming as a contributor to salt sensitivity. In offspring of mothers fed a low protein diet or given dexamethasone during gestation, chloride transport in the thick ascending limb (mTAL) and the lumen positive transepithelial potential difference were significantly higher compared to control rats, demonstrating increased bumetanide sensitive Na^+-K^+-2 Cl^- (NKCC2) transporter activity in the mTAL.[177] Rats were already hypertensive at the time of study and, consistent with these findings, administration of furosemide reduced blood pressure in the prenatal low protein diet group compared to controls, demonstrating that the increased NKCC2 activity was contributing to the higher blood pressure.[177] Interestingly, in this study, at 6 weeks of age, expression of the NKCC2 was increased in the medulla of the low protein diet group but not the prenatal dexamethasone group, despite changes in sodium chloride transport being evident in both.[177] Similarly, NKCC2 and thiazide sensitive Na^+-Cl^- cotransporter (NCC) protein levels were significantly elevated in low birth weight, induced by maternal low protein diet, rat kidneys at 4 weeks of age—that is, before the manifestation of hypertension. This occurred even though expression of the proximal tubule sodium hydrogen exchanger (NHE3) and the epithelial sodium channel (ENaC) expression were not changed.[178]

In another study, prenatal dexamethasone was associated with increased NKCC2 protein expression at 8 weeks, along with NCC and NHE3, but not ENaC, and their expression was reduced by renal denervation, suggesting modulation of sodium transporter expression by the renal nerves.[179] Other investigators found mRNA expression of the glucocorticoid receptor, and the glucocorticoid responsive α1- and β1-subunits of Na^+/K^+-ATPase to be increased in offspring of rats fed low protein diets during gestation.[180] Similarly, in animals subjected to maternal diabetes, renal Na^+/K^+-ATPase expression was increased, as well as the β and γ subunits of ENaC.[168] When these animals were subjected to a high salt diet, expression of NHE3 and NCC increased, but expression of NKCC2 decreased.[168] In yet another model of low nephron endowment, there was no difference in NCC or ENaC expression by immunohistochemistry in kidneys of Gdnf heterozygous compared to wild type mice.[119] Various programming models of low nephron number and hypertension, therefore, are associated with some disparities in renal sodium transporter expression, but in general it appears sodium transporters are upregulated and likely contribute to increased blood pressures. Whether the alteration in sodium transport is a direct result of reduced nephron numbers, single nephron hyperfiltration and glomerulotubular balance, or is an independent simultaneously programmed change in the renal tubules is not yet clear.

The intrarenal renin-angiotensin system is important for nephrogenesis as well as blood pressure regulation.[8,72] Administration of inhibitors of the renin-angiotensin system during renal development results in abnormal kidneys and reduced nephron numbers.[8] Maternal low protein diet, prenatal dexamethasone, and uterine artery ligation all induce intrauterine growth restriction and have been associated with altered expression of components of the renin-angiotensin system.[8,181–185] The observed alterations in renal renin, angiotensinogen, angiotensin converting enzyme activity, angiotensin II, and angiotensin receptor subtype 1 and 2 levels all appear to be modulated at different times of development with some changes being present at birth and others manifesting in later life, as reviewed elsewhere.[8] In addition, some of the observed variation likely results from differences in timing and nature of the programming insult. The observation that programmed hypertension could be modulated by postnatal administration of inhibitors of the renin-angiotensin system supports a role for this system in generation of increased blood pressures, potentially involving altered sodium transport, reduced nitric oxide activity, and reactive oxygen species generation.[183,185] Furthermore, evidence of lack of suppression of this system in the setting of increased renal sodium transport and plasma volume expansion also suggests dysregulation by prenatal programming.[8] To our knowledge, levels of renin-angiotensin system activity have not been investigated in low birth weight humans.

Catch-up Growth and Blood Pressure

Developmental programming does not only encompass the intrauterine period but, as discussed previously, early postnatal events may also be critical in renal development. Similarly, early childhood growth, especially after intrauterine growth restriction, is emerging as a significant risk factor for subsequent hypertension and cardiovascular disease.[186]

In low birth weight male rats with reduced nephron numbers, induced by maternal gestational protein restriction, postnatal overfeeding resulted in accelerated development of hypertension and a significant reduction in GFR in adulthood.[187] The rapid postnatal weight gain in the low birth weight overfed rats therefore exacerbated the programmed risk of hypertension, acting as a "second hit" superimposed on the low nephron number. Interestingly, appetite, obesity, and energy expenditure are also developmentally programmed, compounding the risk of cardiovascular disease in growth restricted individuals.[188] In a cohort of adolescents, rapid weight gain in the first 2 weeks of life was associated with reduced flow-mediated dilation of the brachial artery measured at ages 13 to 16, underscoring the long-term impact of early nutrition on vascular function.[189] Similarly, weight gain within the first 5 months of life was associated with increased systolic and diastolic blood pressures at 25 years of age, although only systolic blood pressure was inversely associated with birth weight.[190] The combination of low birth

2.5 Difference in Systolic Blood Pressure (mm Hg) at 22 Years per SDs Increase in Birth Weight, Infant Weight Gain (First Year), and Early Childhood Weight Gain (1–5 Years)[a]

Weight Growth Variable	Regression Coefficient (95% CI)	
	Without Adjustment for Adult BMI	With Adjustment for Adult BMI
Birth weight	−1.3 (−2.3 to −0.3)	−1.2 (−2.2 to −0.3)
Conditional infant weight gain	0.5 (−0.6 to 1.5)	−0.1 (−1.2 to 0.9)
Conditional early childhood weight gain	1.6 (0.6 to 2.7)	0.6 (−0.5 to 1.7)
Adult BMI[b]	. . .	2.6 (1.5 to 3.7)

[a]With and without adjustment for adult body mass index.
[b]Geometric SDs.
CI, confidence interval; BMI, body mass index; SDs, standard deviations.
Reprinted with permission from Law CM, Shiell AW, Newsome CA, et al. Fetal, infant, and childhood growth and adult blood pressure: a longitudinal study from birth to 22 years of age. Circulation. 2002;105:1088–1092.

weight followed by accelerated childhood growth has also been consistently found to be associated with higher blood pressures in childhood and adulthood (Table 2.5).[191,192]

Several potential mechanisms have been investigated to explain this amplification of cardiovascular risk by rapid weight gain after growth restriction. In obese sheep that had been exposed to maternal nutrient restriction during gestation, adipose tissue showed an increase in number of necrotic cells, increased secretion of pro-inflammatory factors, and increased evidence of endoplasmic reticulum stress compared to obese controls.[188] In addition, the nutrient restricted obese sheep exhibited abnormal myocardial structure and function.[188] One possible connection between growth restriction and accelerated catch-up growth is the development of premature senescence.[193] Chronic diseases such a hypertension, chronic kidney disease, and cardiovascular disease have all been associated with increased expression of senescence markers. In animal models, low birth weight followed by accelerated postnatal growth was associated with more rapid telomere shortening and accelerated senescence in kidneys and aortas, as well as premature death.[194–196] These markers were not correlated directly with blood pressures and nephron numbers in the same animals. However, investigators utilized a standard programming model of maternal dietary protein restriction, therefore low birth weight animals were expected to have low nephron numbers and high blood pressures.

In another study, there was no difference in expression of the senescence marker p16 between low birth weight and normal birth weight rats, suggesting that senescence is not likely a contributor to the reduced nephron numbers.[193] p16 was significantly increased by weaning in kidneys and hearts of low birth weight rats, and continued to rise progressively with age, suggesting ongoing tissue stress and accelerated senescence precipitated by catch-up growth. Increased senescence in the low birth weight kidneys may result from ongoing hyperfiltration injury in kidneys with fewer nephrons, exacerbated by a rapid increase in body size. Interestingly in humans, leukocyte telomere length was not different between small for gestational age and appropriate for gestational age newborns, but by 5 years low birth weight children had significantly shorter telomeres than normal birth weight children, consistent with accelerated senescence.[197,198] However, growth trajectories of these children were not reported. Markers of endoplasmic reticulum and mitochondrial stress were increased in low birth weight rat kidneys after rapid catch-up growth, which points to increased reactive species generation as a possible mediator of increased senescence.[193] Consistent with these animal findings, in humans there is evidence of increased oxidative stress in children born small for gestational age compared to controls, which was relatively higher in those who experienced catch-up growth.[199,200] The link between nephron mass, catch-up growth, premature senescence, and the development of hypertension and renal disease in humans after developmental programming has not been studied.

Renal Function and Nephron Mass

Glomerular Filtration Rate

A reduction in nephron number, and therefore filtration surface area, in the absence of compensatory hyperfiltration, would be expected to be associated with a reduced whole kidney GFR. Consistent with this possibility, amikacin clearance, as a surrogate for GFR, was lower in premature or growth restricted neonates on day 1 of life (i.e., before

any adaptation would have occurred).[201] Similarly, nephron number and GFR were measured in newborn growth restricted piglets.[202] GFR was reduced in proportion with nephron number, suggesting a lack of glomerular adaptation early after birth. With increasing age, however, as the single nephron GFR increased with hyperfiltration, differences in total GFR have not been consistently seen between normal and low birth weight subjects. Among 6- to 12-year-olds, estimated creatinine clearance was lower and serum creatinine higher in very low birth weight compared to age-matched normal birth weight subjects.[203] In contrast, estimated GFRs were not different between three groups of 9- to 12-year-olds born with low gestational age or either small for gestational age or appropriate for gestational age at term.[106] Interestingly, estimated GFR calculated using cystatin C showed a significant linear trend with birth weight compared to creatinine-based GFR in a cohort of children divided into quartiles by birth weight. This suggested the potential pitfalls with creatinine measurements and/or the need to adapt GFR calculation formulae in young low birth weight subjects.[204]

Utilizing iothalamate clearance, GFR was measured in a cohort of children at a mean age of 7.6 years who were born with a birth weight under 1,000 g or before 30 weeks of gestation, and stratified according to whether they had experienced either intrauterine or extrauterine growth restriction or normal perinatal nutrition.[55] GFRs were significantly lower in both pre- and postnatally growth restricted children, although still within the normal range for their age. This observation further highlights the potential negative impact of poor extrauterine nutrition on early renal development in premature infants. In young adults born very premature, the creatinine-based Cockroft-Gault GFR was found to correlate positively with birth weight.[131] GFRs measured by 24-hour urine creatinine clearance within adult twin pairs were lower in the lower birth weight twin, again suggesting an independent effect of the intrauterine environment on programming of renal function.[205] Overall, from several studies, GFRs were estimated to increase by 3.8 to 7.2 mL per minute in males and 2.6 to 5.7 mL per minute in females per 1-kg increase in birth weight.[206,207]

An interesting small study evaluated total GFR, effective renal plasma flow, and filtration fraction before and after low dose dopamine or an oral amino acid load to test renal functional reserve in 20-year-olds born (1) premature with appropriate weight for gestational age, (2) premature and small for gestational age, or (3) term and appropriate for gestational age. Intriguingly, although the changes did not reach statistical significance, the stimulated increase in GFR was less in small for gestational age compared with appropriate for gestational age and control subjects. Effective renal plasma flow was lower in both small for gestational age and appropriate for gestational age preterm subjects, suggesting at least a small decrease in renal functional reserve capacity.[208]

GFR and effective renal plasma flow were also studied before and after an intravenous amino acid infusion in young adults who had diabetic mothers (i.e., had been exposed to maternal diabetes during gestation) compared to those with diabetic fathers. Subjects were matched for age, gender, BMI, and birth weight. The offspring of diabetic mothers had a significantly reduced renal reserve capacity, suggesting a renal programming effect due to maternal diabetes.[53] Evaluation of renal functional reserve may therefore be a sensitive method to detect subtle changes in renal function due to a reduced nephron number that may not be evident with baseline GFR measurements.

Proteinuria is a marker of glomerular hyperfiltration and renal injury and, as such, has been investigated in several low birth weight populations. Among children aged 8 to 11 years of age, low birth weight was associated with significantly higher blood pressures and 24-hour urine albumin excretion compared to normal birth weight controls.[209] Multiple other studies have also shown a largely consistent relationship between low birth weight and proteinuria, although in some studies albuminuria was associated with thinness at birth, an indicator of intrauterine stress, rather than birth weight.[94,131,207,210,211] Among Australian Aborigines, albuminuria was strongly associated with low birth weight and the relationship was amplified with increasing age.[212] Macroalbuminuria in this cohort was also associated with a high risk of renal failure and death.[213] In a Finnish population with type 1 diabetes, however, after a mean duration of diabetes of 19 years, no association was found between proteinuria and birth weight stratified as low, <10th percentile; high, >90th percentile; and intermediate, between 10th and 90th percentiles.[214]

In a similar study, among Danish women with type 1 diabetes, with a median duration of 27 years, 75% of those with birth weight under the 10th percentile had nephropathy, defined as persistent urine albumin excretion >300 g per day, compared with 35% of those with birth weights above the 90th percentile.[215] The effect was not present in men, although in another study, short stature in men was associated with a higher risk of macroalbuminuria.[216] A U-shaped association between birth weight and proteinuria was found among Pima Indians with type 2 diabetes in the United States, suggesting that high birth weight and low birth weight are both risk factors for renal disease in this population.[94] Interestingly 64% of subjects with high birth weight were offspring of diabetic mothers versus none of those with low birth weight. The association of high birth weight with proteinuria was lost after adjustment for maternal diabetes, suggesting potentially different programming mechanisms in low birth weight and high birth weight with respect to proteinuria.[94]

Differences between these studies in diabetic subjects may reflect altered genetic susceptibility to renal disease in the Pima population, differences between type 1 and type 2 diabetes, as well as different durations of diabetes. As mentioned previously, podocyte abnormalities are present in kidneys with developmentally programmed low nephron numbers, which may contribute to the development of proteinuria in low birth weight subjects.[118]

Chronic Kidney Disease

Although GFRs have been found to be statistically lower in low birth weight populations, this has not always been outside of the normal range, calling into the question true clinical relevance.[55,131] A recent meta-analysis examined 31 studies that reported risk of CKD—including various end points, including proteinuria, diabetic nephropathy, and reduced GFR—relative to birth weight.[207] Overall they found a 70% increased risk of CKD in low birth weight individuals, regardless of end point studied.[207] Again, the effect was stronger in males. Among 12,364 participants in the Kidney Early Evaluation Program, among men a U-shaped curve was found for risk of CKD, defined as an estimated GFR <60 mL per minute or albumin excretion ≥30 g per g, and birth weight, with increased risk with birth weights <2,500 g and ≥4,500 g.[73] No association was found among female participants, however.

The clinical relevance of the risk of CKD with low or high birth weights is borne out in studies examining risk of ESRD. Retrospective analysis in over 2 million Norwegians found the relative risk of ESRD to be 1.7 in males and females born below the 10th percentile in weight.[217] Interestingly, when looking at absolute birth weights and risk, the relative risk for ESRD was 2.0 with birth weights <2.5 kg, but was only increased in females with birth weights ≥4.5 kg.[217] In a predominantly black, southern U.S. population, a U-shaped curve was again described for risk of ESRD with low and high birth weights, this time in both men and women.[218]

Growing numbers of epidemiologic studies therefore support the relationship between high birth weight or low birth weight and risk of subsequent renal disease (Table 2.6). A direct link between nephron number and renal disease in individual human subjects has not been made, however. Nephron number is unlikely to be the sole cause of renal dysfunction in most patients, and other susceptibilities likely compound the risk. A low nephron number, however, may lower the threshold to reach a critical loss of renal function in response to superimposed renal injury or stress. In support of this possibility, low birth weight has been associated with poorer renal outcomes in patients with nephrotic syndrome, membranous nephropathy, IgA nephropathy, minimal change disease, and diabetic nephropathy.[95,219–222]

Interestingly in a model of diabetes superimposed on low nephron number, the increase in glomerular volume in response to hyperglycemia was more exaggerated and maladaptive in the low compared to normal birth weight rats.[223] Similarly, mesangioproliferative glomerulonephritis was associated with significantly increased glomerulosclerosis in low birth weight animals with reduced nephron numbers.[224] Potential molecular mechanisms whereby kidneys with fewer nephrons adapt differently than normal kidneys include an imbalance between apoptosis and cell proliferation, accelerated senescence, reactive oxygen species generation, and mitochondrial dysfunction.[162,193]

RELEVANCE OF NEPHRON MASS IN TRANSPLANTATION

Impact of Kidney Donation

In experimental models of low birth weight, as described previously, nephron numbers are often reduced by 25% to 30%, and animals develop spontaneous hypertension and

2.6 Clinical Findings Associated with Birth Weight, Nephron Number, and Kidney Size in Humans

Low Birth Weight/ Prematurity	Low Nephron Number	Reduced Renal Size	High Birth Weight/ Maternal Diabetes
↑ Blood pressure[127] Salt sensitivity[105,176] Proteinuria[131,210] ↓ GFR[55,131,201] ↓ Renal functional reserve[208] Accelerated progression of primary renal disease[219–222] Chronic kidney disease[73,207] End-stage kidney disease[217,218] Death[210]	↑ Blood pressure[70] ↑ Glomerular volume[13] ? Predisposition to renal failure in neonates[54]	↑ Blood pressure[105] Salt sensitivity[105] ↓ GFR[105] ↓ Renal allograft survival if small kidney into large recipient[237]	Proteinuria[95] ↓ Renal functional reserve[53] End-stage kidney disease[217,218]

↑, increase; ↓, decrease; ?, unknown.

renal dysfunction.[12,37] In humans, donation of a kidney implies loss of 50% of nephron mass, and therefore may carry some long-term risk. However, many studies have shown that kidney donation is safe and former kidney donors have similar or even better life expectancy and lower risk for ESRD than the general population.[153] This paradox might be due to the very thorough screening of potential donors and the selection of only the very healthiest subjects. In addition, the studies on long-term outcomes have predominantly been done in Caucasians, are limited by significant loss to follow-up, and do not use similarly selected, healthy control groups for their comparative analysis.

An early retrospective study of 52 kidney donors followed after at least 10 years did find a higher risk of hypertension and mild proteinuria compared to age-matched controls and other potential donors, although creatinine clearance did not deteriorate as a function of time.[225] Interestingly the risks of hypertension and proteinuria were greater in men. In contrast, subsequent studies in predominantly Caucasian donors did not find a significantly increased risk of hypertension and proteinuria, suggesting that uninephrectomy is safe.[153] Concerns have been raised, however, about possible harm of living kidney donation in other ethnic groups. After a median of 16 years postdonation, the incidence of new onset hypertension, CKD, and ESRD was significantly higher among Australian Aboriginal kidney donors compared to Caucasians.[226] Similarly, among Canadian donors, hypertension was present in 42% of Aboriginals compared with 19% of Caucasians by a mean of 14 years of follow-up, and in 100% of Aboriginal donors by 20 years postdonation.[227] Estimated GFR was not different between Caucasians and Aboriginals, but proteinuria was more common among Aboriginal donors. In U.S. cohorts, black kidney donors were found to have significantly more hypertension and CKD compared to white donors.[159,228]

In all of these cohorts donors are presumed to have been screened and found healthy prior to donation, therefore, uninephrectomy in populations with high susceptibility to hypertension and kidney disease may carry more risk than has thus far been appreciated. Aboriginal Australian and U.S. black populations have lower birth weights than their Caucasian counterparts, and Canadian Aboriginals have higher birth weights (World Health Organization). This suggests that programming of nephron number may be a factor contributing to increased hypertension and renal risk postnephrectomy. Birth weight and early development history should therefore be incorporated into a potential donor's evaluation, and consideration given to measurement of renal functional reserve, although at present it is likely premature to suggest that decisions on donor eligibility be based on this information.

Impact on Allograft Function

The importance of nephron mass as a nonimmunologic determinant of long-term transplant outcomes has been debated since the nephron number hypothesis was first put forward.[229] Indeed, in rat models it has been elegantly shown that transplanted nephron mass (i.e., kidneys with varying nephron numbers) has a significant impact on allograft outcome, independent of immunologic barriers.[230] As nephron numbers cannot be determined in vivo, various surrogates have been examined in humans to assess the impact of transplanted nephron mass, measurable to some degree ex vivo, relative to recipient demand, on allograft outcomes (Table 2.7). Such surrogates include ratios of recipient to donor body surface area (BSA) or body weight, of kidney volume to recipient BSA, and of kidney weight to recipient body weight.[231–235] As mentioned previously, kidney mass and kidney volume do reflect nephron number to some degree, but these data should be interpreted with caution, realizing that BSA is not always proportional to kidney weight, and that two kidneys of the same size may differ in nephron number.

Despite these caveats and the variability of methods employed, the evidence shows fairly consistently that small kidneys, or kidneys from small donors, transplanted into larger recipients, tend to have poorer outcomes.[231–235] Duration of follow-up, however, is also a crucial variable, as seen in the donor literature, where differences in hypertension and proteinuria emerge only after many years. Interestingly, an early report in a cohort of renal allograft recipients, with a mean of 32 months of follow-up, failed to find any impact of graft weight on short-term graft survival.[236] With longer follow-up, however, in the same cohort, subjects with a low donor kidney weight to recipient body weight ratio (DKW/RBW) showed a greater adaptive early increase in GFR, which remained stable for 7 years, followed by a more rapid loss of GFR as compared to the high DKW/RBW group, thus demonstrating the importance of long term follow-up.[237] These data suggest that smaller kidneys transplanted into larger recipients underwent early hyperfiltration that could not be sustained indefinitely, resulting in ongoing nephron loss. Over time, the low DKW/RBW group required more antihypertensives, had more proteinuria, and on kidney biopsy showed a greater degree of glomerulosclerosis. Overall, the risk of transplant failure was 55% higher in low DKW/RBW compared to the high DKW/RBW group at 2 years.[237] The authors conclude that mismatch between allograft and recipient weight is an independent predictor of long-term graft survival.

These results are consistent with another analysis, which was restricted to recipients of living donor kidneys who had not experienced any complications within the first year of transplantation. Progressively higher levels of urine protein excretion and lower GFRs occurred as DKW/RBW fell.[238] Similarly, a large retrospective analysis of 32,083 recipients of a first cadaveric kidney transplant, utilizing the ratio of donor to recipient BSA, found that large recipients of small kidneys had a 43% increased risk of late allograft failure compared to the reference group which was medium sized recipients receiving kidneys from medium sized donors.[234]

Another study examined the outcomes of kidneys from donors over age 60, presumed to have fewer nephrons by

2.7 Impact of Donor and Recipient Mismatch on Renal Allograft Outcomes

Measurement	Allograft Outcome	Donor	Reference
Donor kidney weight : recipient body weight	↑ Risk of late allograft loss, proteinuria, hypertension, and glomerulosclerosis at 6.2 years with lower ratios	Cadaveric	237
Donor kidney weight : recipient body weight	↓ Creatinine clearance and ↑ proteinuria at 3 years with lower ratios	Living	238
Donor–recipient body weight ratio	↓ Graft survival at 5 years in low ratio group	Living	232
Donor : recipient BSA	↑ Late allograft loss in large recipients who received kidneys from small donors	Cadaveric	234[a]
Transplant cross-sectional area (ultrasound): recipient body weight (Tx/W)	↓ Creatinine, trend toward improved outcome with larger ratios at 12 months	Cadaveric	241
Kidney weight (g)	↑ Creatinine clearance with higher kidney weight at 12 months	Living	231

[a]More studies reviewed in this reference.
↑, increase; ↓, decrease; BSA, body surface area.

virtue of increased age, relative to recipient BMI, and found that 5-year allograft survival was significantly lower in recipients with higher BMI or BSA, again suggesting an impact for mismatch between fewer transplanted functioning nephrons and higher donor demand on long-term outcomes.[239] Not all studies have found consistent results, however, with some failing to find an impact of differing donor to recipient BSA ratios on outcomes of paired cadaver kidneys.[233] The high and low ratios did overlap in this study, however.

A more recent study of paired kidneys did find a donor–recipient size mismatch to be a risk factor for delayed graft function.[240] Other investigators have examined the ratio of transplanted kidney cross-sectional area, as measured by ultrasound, relative to recipient weight as a predictor of outcomes. They found lower serum creatinines and a trend toward improved graft survival at 5 years in those with higher ratios.[241] Overall, therefore, transplanted nephron mass does appear to have a long-term impact on allograft function. Clinically, however, nephron mass at transplantation is likely impacted by many other factors in addition to nephron endowment (e.g., loss through peritransplant injury, immune-mediated injury, donor age, and other donor factors). Kidneys transplanted with fewer nephrons are likely to have less functional reserve and therefore are at risk of declining function over time. Awareness of this association may impact a clinician's decision about medication choices, peritransplant interventions, and ultimately potentially organ allocation.

THE IMPACT OF PROGRAMMING ON RELATED ORGAN SYSTEMS

The interaction of gestational diabetes exposure, birth weight, and proteinuria, for example, demonstrates that developmental programming may impact multiple organ systems simultaneously.[53,95,215] In a Swedish cohort of 18,230 twins, low birth weight was found to increase the risk of adult type 2 diabetes with an adjusted odds ratio of 1.44 per 500 g decrease in birth weight.[242] Similarly, in a Chinese cohort, low birth weight was found to be inversely associated with risk of type 2 diabetes, and both high and low birth weights were associated with increased risk of hypertension and abdominal obesity.[243] Low birth weight combined with abdominal obesity was the strongest predictor of diabetes. Obesity and diabetes are both risk factors for CKD and, therefore, their interaction with low birth weight likely augments this risk. Interestingly, low birth weight rats, induced by maternal low protein diet, suffered more severe cardiac dysfunction after myocardial ischemia and reperfusion compared to normal birth weight rats.[244] In another study, graded surgical reduction in nephron number in normal rats was associated with progressively

higher systolic blood pressures, left ventricular hypertrophy, and left ventricular systolic and diastolic dysfunction compared to sham operated controls.[245] In sheep, fetal uninephrectomy resulted in hypertension and more severe renal dysfunction and albuminuria with age.[156] In addition, cardiac functional reserve, measured in response to dobutamine infusion, was significantly reduced by 6 months of age in the neonatally nephrectomized sheep and left ventricular mass was significantly increased. In the clinical arena, patients with CKD often have coexisting diabetes and/or cardiac dysfunction, and CKD itself is a known cardiac risk factor. Whether some of this association is related to the consequences of renal dysfunction per se—that is, hypertension, volume expansion, proteinuria—or may reflect parallel programming of multiple organ systems in the same individual has yet to be elucidated.

CONCLUSION

The concept that nephron mass, at least in part, is determined during the perinatal period and has a long-term impact on an individual's subsequent risk of hypertension and renal disease is now accepted (Fig. 2.10). Nephron number alone is not often enough to result in overt disease, but does appear to be a strong modifier of risk in various ethnic groups, as well as under certain clinical conditions (e.g., diabetes mellitus). As such, surrogate markers for low nephron number and adverse perinatal conditions should be screened for in the clinical setting and appreciated as risk factors that may not be modifiable in the adult. However, they may highlight the need to minimize further insults and optimize other risk factors for hypertension and renal disease. Low birth weight is currently the most useful clinical surrogate for low nephron mass and the developmentally determined risk of hypertension and renal disease.

Much more work is needed to determine the impact of high birth weight. The exciting experimental findings that low nephron numbers can be rescued under some circumstances points to the importance of improving maternal health before and during gestation, optimizing of neonatal nutrition, and avoiding nephrotoxins in the early perinatal period, as well as raising hope for potential translation of therapeutic interventions to the human in the future. From a public health point of view, close attention should be paid to improving perinatal care and early childhood nutrition as potential tools to stem the growing tides of renal and cardiovascular disease in future generations.

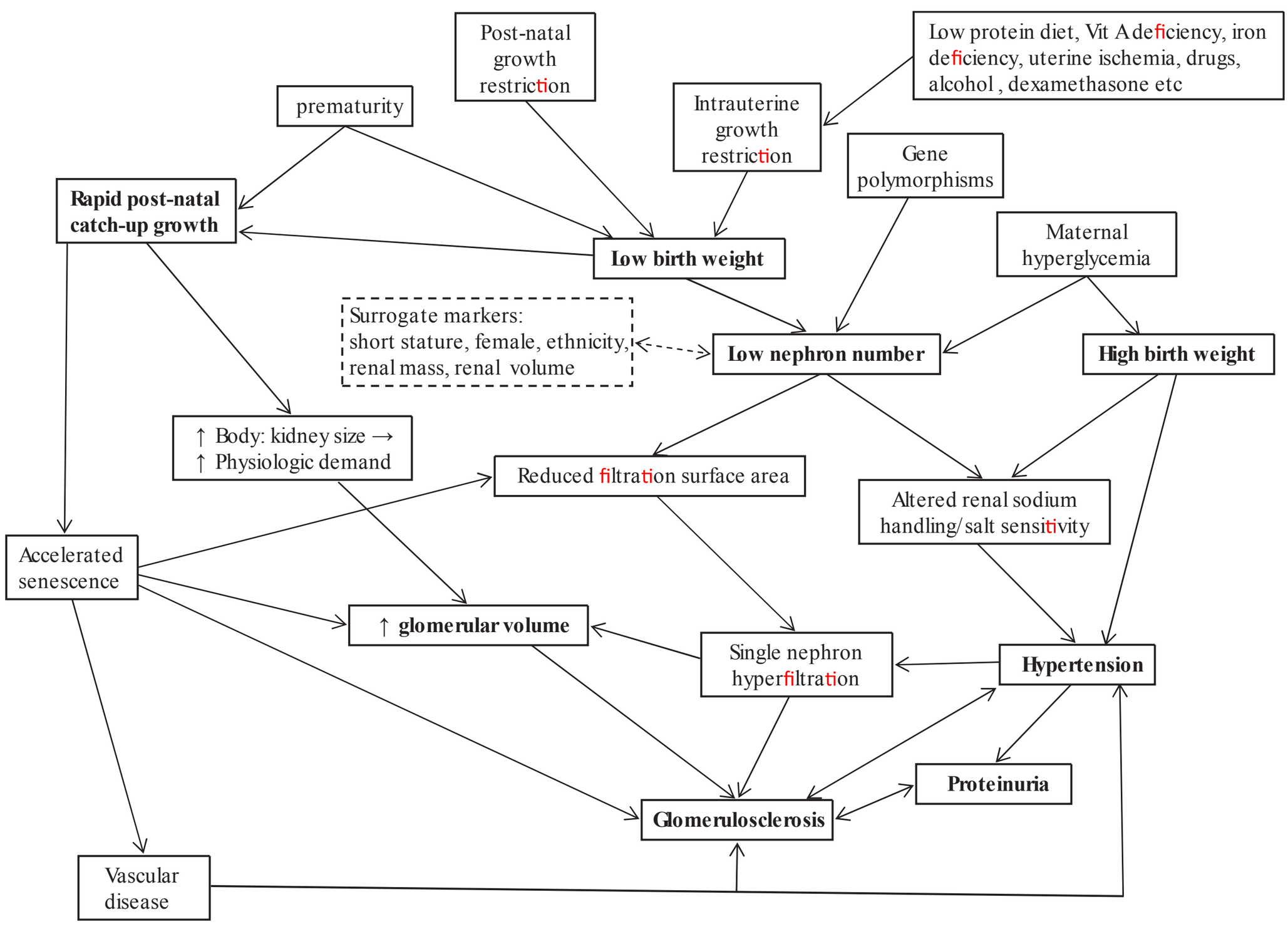

FIGURE 2.10 Diagram of proposed mechanisms impacting developmental programming of renal disease and hypertension. (Adapted from Schreuder M, Delemarre-van de Waal H, van Wijk A. Consequences of intrauterine growth restriction for the kidney. *Kidney Blood Press Res*. 2006;29:108–125.)

REFERENCES

1. Guyton AC, Coleman TG, Young DB, et al. Salt balance and long-term blood pressure control. Annu Rev Med. 1980;31:15–27.
http://www.ncbi.nlm.nih.gov/pubmed/6994602

2. Brenner BM, Garcia DL, Anderson S. Glomeruli and blood pressure. Less of one, more the other? Am J Hypertens. 1988;1:335–347.
http://www.ncbi.nlm.nih.gov/pubmed/3063284

3. McMillen IC, Robinson JS. Developmental origins of the metabolic syndrome: prediction, plasticity, and programming. Physiol Rev. 2005;85:571–633.
http://www.ncbi.nlm.nih.gov/pubmed/15788706

4. Hsu CY, Lin F, Vittinghoff E, et al. Racial differences in the progression from chronic renal insufficiency to end-stage renal disease in the United States.J Am Soc Nephrol. 2003;14:2902–2907.

5. Fan Z, Lipsitz S, Egan B, et al. The impact of birth weight on the racial disparity of end-stage renal disease. Ann Epidemiol. 2000;10:459.
http://www.ncbi.nlm.nih.gov/pubmed/11018370

6. Fan ZJ, Lackland DT, Kenderes B, et al. Impact of birth weight on familial aggregation of end-stage renal disease. Am J Nephrol. 2003;23:117–120.
http://www.ncbi.nlm.nih.gov/pubmed/12481151

7. Lackland DT, Egan BM, Syddall HE, et al. Associations between birth weight and antihypertensive medication in black and white Medicaid recipients. Hypertension. 2002;39:179–183.
http://www.ncbi.nlm.nih.gov/pubmed/11799099

8. Baum M. Role of the kidney in the prenatal and early postnatal programming of hypertension. Am J Physiol Renal Physiol. 2010;298:F235–247.

9. Hoy WE, Hughson MD, Bertram JF, et al. Nephron number, hypertension, renal disease, and renal failure. J Am Soc Nephrol. 2005;16:2557–2564.
http://www.ncbi.nlm.nih.gov/pubmed/16049069

10. Keller G, Zimmer G, Mall G, et al. Nephron number in patients with primary hypertension. N Engl J Med. 2003;348:101–108.
http://www.ncbi.nlm.nih.gov/pubmed/12519920

11. Schreuder MF, Langemeijer ME, Bokenkamp A, et al. Hypertension and microalbuminuria in children with congenital solitary kidneys. J Paediatr Child Health. 2008;44:363–368.
http://www.ncbi.nlm.nih.gov/pubmed/18476930

12. Vehaskari VM, Aviles DH, Manning J. Prenatal programming of adult hypertension in the rat. Kidney Int. 2001;59:238–245.
http://www.ncbi.nlm.nih.gov/pubmed/11135076

13. Puelles VG, Hoy WE, Hughson MD, et al. Glomerular number and size variability and risk for kidney disease. Curr Opin Nephrol Hypertens. 2011;20:7–15.

14. Fonseca Ferraz ML, Dos Santos AM, Cavellani CL, et al. Histochemical and immunohistochemical study of the glomerular development in human fetuses. Pediatr Nephrol. 2008;23:257–262.
http://www.ncbi.nlm.nih.gov/pubmed/17990004

15. Bertram JF. Counting in the kidney. Kidney Int. 2001;59:792–796.
http://www.ncbi.nlm.nih.gov/pubmed/11168963

16. Nyengaard JR. Stereologic methods and their application in kidney research. J Am Soc Nephrol. 1999;10:1100–1123.
http://www.ncbi.nlm.nih.gov/pubmed/10232698

17. Basgen JM, Steffes MW, Stillman AE, et al. Estimating glomerular number in situ using magnetic resonance imaging and biopsy. Kidney Int. 1994;45:1668–1672.
http://www.ncbi.nlm.nih.gov/pubmed/7933814

18. Nyengaard JR, Bendtsen TF. Glomerular number and size in relation to age, kidney weight, and body surface in normal man. Anat Rec. 1992;232:194–201.
http://www.ncbi.nlm.nih.gov/pubmed/1546799

19. Hughson M, Farris AB, Douglas-Denton R, et al. Glomerular number and size in autopsy kidneys: The relationship to birth weight. Kidney Int. 2003;63:2113–2122.

20. Hoy WE, Douglas-Denton RN, Hughson MD, et al. A stereological study of glomerular number and volume: preliminary findings in a multiracial study of kidneys at autopsy. Kidney Int. 2003:S31–S37.

21. Moritz KM, Wintour EM, Black MJ, et al. Factors influencing mammalian kidney development: implications for health in adult life. Adv Anat Embryol Cell Biol. 2008;196:1–78.

22. Luyckx VA, Brenner BM. Nephron endowment. In: Brenner BM, ed. The Kidney, 9th ed. Philadelphia: Elsevier; 2011.

23. Lucas SR, Costa Silva VL, Miraglia SM, et al. Functional and morphometric evaluation of offspring kidney after intrauterine undernutrition. Pediatr Nephrol. 1997;11:719–723.
http://www.ncbi.nlm.nih.gov/pubmed/9438651

24. Langley-Evans S, Langley-Evans A, Marchand M. Nutritional programming of blood pressure and renal morphology. Arch Physiol Biochem. 2003;111:8–16.
http://www.ncbi.nlm.nih.gov/pubmed/12715270

25. Lisle SJ, Lewis RM, Petry CJ, et al. Effect of maternal iron restriction during pregnancy on renal morphology in the adult rat offspring. Br JNutr. 2003;90:33–39.

26. Hoppe CC, Evans RG, Bertram JF, et al. Effects of dietary protein restriction on nephron number in the mouse. Am J Physiol Regul Integr Comp Physiol. 2007;292:R1768–R1774.

27. Bryce J, Coitinho D, Darnton-Hill I, et al. Maternal and child undernutrition: effective action at national level. Lancet. 2008;371:510–526.
http://www.ncbi.nlm.nih.gov/pubmed/18206224

28. Merlet-Benichou C, Vilar J, Lelievre-Pegorier M, et al. Role of retinoids in renal development: pathophysiological implication. Curr Opin Nephrol Hypertens. 1999;8:39–43.
http://www.ncbi.nlm.nih.gov/pubmed/9914859

29. Goodyer P, Kurpad A, Rekha S, et al. Effects of maternal vitamin A status on kidney development: a pilot study. Pediatr Nephrol. 2007;22:209–214.
http://www.ncbi.nlm.nih.gov/pubmed/17093988

30. Sutherland MR, Gubhaju L, Yoder BA, et al. The effects of postnatal retinoic acid administration on nephron endowment in the preterm baboon kidney. Pediatr Res. 2009;65:397–402.
http://www.ncbi.nlm.nih.gov/pubmed/19092718

31. Bhat PV, Manolescu DC. Role of vitamin A in determining nephron mass and possible relationship to hypertension. J Nutr. 2008;138:1407–1410.
http://www.ncbi.nlm.nih.gov/pubmed/18641182

32. Wlodek ME, Westcott K, Siebel AL, et al. Growth restriction before or after birth reduces nephron number and increases blood pressure in male rats. Kidney Int. 2008;74:187–195.
http://www.ncbi.nlm.nih.gov/pubmed/18432184

33. Moritz KM, Mazzuca MQ, Siebel AL, et al. Uteroplacental insufficiency causes a nephron deficit, modest renal insufficiency but no hypertension with ageing in female rats. J Physiol. 2009;587:2635–2646.
http://www.ncbi.nlm.nih.gov/pubmed/19359373

34. Kajantie E, Dunkel L, Turpeinen U, et al. Placental 11 beta-hydroxysteroid dehydrogenase-2 and fetal cortisol/cortisone shuttle in small preterm infants. J Clin Endocrinol Metab. 2003;88:493–500.

35. Habib S, Gattineni J, Twombley K, et al. Evidence that prenatal programming of hypertension by dietary protein deprivation is mediated by fetal glucocorticoid exposure. Am J Hypertens. 2011;24(1):96–101.

36. Wintour EM, Moritz KM, Johnson K, et al. Reduced nephron number in adult sheep, hypertensive as a result of prenatal glucocorticoid treatment. J Physiol. 2003;549:929–935.
http://www.ncbi.nlm.nih.gov/pubmed/12730337

37. Celsi G, Kistner A, Aizman R, et al. Prenatal dexamethasone causes oligonephronia, sodium retention, and higher blood pressure in the offspring. Pediatr Res. 1998;44:317–322.
http://www.ncbi.nlm.nih.gov/pubmed/9727707

38. Bramlage CP, Schlumbohm C, Pryce CR, et al. Prenatal dexameth asone exposure does not alter blood pressure and nephron number in the young adult marmoset monkey. Hypertension. 2009;54:1115–1122.
http://www.ncbi.nlm.nih.gov/pubmed/19770406

39. Schreuder MF, Bueters RR, Huigen MC, et al. Effect of drugs on renal development. Clin J Am Soc Nephrol. 2011;6:212–217.
http://www.ncbi.nlm.nih.gov/pubmed/21071516

40. Kent AL, Douglas-Denton R, Shadbolt B, et al. Indomethacin, ibuprofen and gentamicin administered during late stages of glomerulogenesis do not reduce glomerular number at 14 days of age in the neonatal rat. Pediatr Nephrol. 2009;24:1143–1149.

41. Komhoff M, Wang JL, Cheng HF, et al. Cyclooxygenase-2.selective inhibitors impair glomerulogenesis and renal cortical development. Kidney Int. 2000;57:414–422.
http://www.ncbi.nlm.nih.gov/pubmed/10652018

42. Nathanson S, Moreau E, Merlet-Benichou C, et al. In utero and in vitro exposure to beta-lactams impair kidney development in the rat. J Am Soc Nephrol. 2000;11:874–884.
http://www.ncbi.nlm.nih.gov/pubmed/10770965

43. Tendron-Franzin A, Gouyon JB, Guignard JP, et al. Long-term effects of in utero exposure to cyclosporin A on renal function in the rabbit. J Am Soc Nephrol. 2004;15:2687–2693.

44. Gray SP, Denton KM, Cullen-McEwen L, et al. Prenatal exposure to alcohol reduces nephron number and raises blood pressure in progeny. J Am Soc Nephrol. 2010;21:1891–1902.

45. Gray SP, Kenna K, Bertram JF, et al. Repeated ethanol exposure during late gestation decreases nephron endowment in fetal sheep. Am J Physiol Regul Integr Comp Physiol. 2008;295:R568–574.

46. Valero De Bernabe J, Soriano T, Albaladejo R, et al. Risk factors for low birth weight: a review. Eur J Obstet Gynecol Reprod Biol. 2004;116:3–15.
http://www.ncbi.nlm.nih.gov/pubmed/15294360

47. Vikse BE, Irgens LM, Leivestad T, et al. Preeclampsia and the risk of end-stage renal disease. N Engl J Med. 2008;359:800–809.
http://www.ncbi.nlm.nih.gov/pubmed/18716297

48. Manalich R, Reyes L, Herrera M, et al. Relationship between weight at birth and the number and size of renal glomeruli in humans: a histomorphometric study. Kidney Int. 2000;58:770–773.
http://www.ncbi.nlm.nih.gov/pubmed/10916101

49. Amri K, Freund N, Vilar J, et al. Adverse effects of hyperglycemia on kidney development in rats: in vivo and in vitro studies. Diabetes. 1999;48:2240–2245.
http://www.ncbi.nlm.nih.gov/pubmed/10535460

50. Tran S, Chen YW, Chenier I, et al. Maternal diabetes modulates renal morphogenesis in offspring. J Am Soc Nephrol. 2008;19:943–952.
http://www.ncbi.nlm.nih.gov/pubmed/18305124

51. Magaton A, Gil FZ, Casarini DE, et al. Maternal diabetes mellitus—early consequences for the offspring. Pediatr Nephrol. 2007;22:37–43.
http://www.ncbi.nlm.nih.gov/pubmed/16967284

52. Rocco L, Gil FZ, da Fonseca Pletiskaitz TM, et al. Effect of sodium overload on renal function of offspring from diabetic mothers. Pediatr Nephrol. 2008;23:2053–2060.
http://www.ncbi.nlm.nih.gov/pubmed/18574600

53. Abi Khalil C, Travert F, Fetita S, et al. Fetal exposure to maternal type 1 diabetes is associated with renal dysfunction at adult age. Diabetes. 2010;59(10):2631–2636.

54. Rodriguez MM, Gomez AH, Abitbol CL, et al. Histomorphometric analysis of postnatal glomerulogenesis in extremely preterm infants. Pediatr Dev Pathol. 2004;7:17–25.
http://www.ncbi.nlm.nih.gov/pubmed/17827558

55. Bacchetta J, Harambat J, Dubourg L, et al. Both extrauterine and intrauterine growth restriction impair renal function in children born very preterm. Kidney Int. 2009;76:445–452.

56. Csaicsich D, Russo-Schlaff N, Messerschmidt A, et al. Renal failure, comorbidity and mortality in preterm infants. Wien Klin Wochenschr. 2008;120:153–157.
http://www.ncbi.nlm.nih.gov/pubmed/18365155

57. Askenazi DJ, Griffin R, McGwin G, et al. Acute kidney injury is independently associated with mortality in very low birthweight infants: a matched case-control analysis. Pediatr Nephrol. 2009;24:991–997.
http://www.ncbi.nlm.nih.gov/pubmed/19238451

58. Askenazi DJ, Ambalavanan N, Goldstein SL. Acute kidney injury in critically ill newborns: what do we know? What do we need to learn? Pediatr Nephrol. 2009;24:265–274.

59. Kemper MJ, Muller-Wiefel DE. Renal function in congenital anomalies of the kidney and urinary tract. Curr Opin Urol. 2001;11:571–575.
http://www.ncbi.nlm.nih.gov/pubmed/11734692

60. Dziarmaga A, Clark P, Stayner C, et al. Ureteric bud apoptosis and renal hypoplasia in transgenic PAX2.Bax fetal mice mimics the renal-coloboma syndrome. J Am Soc Nephrol. 2003;14:2767–2774.
http://www.ncbi.nlm.nih.gov/pubmed/14569086

61. Cain JE, Di Giovanni V, Smeeton J, et al. Genetics of renal hypoplasia: insights into the mechanisms controlling nephron endowment. Pediatr Res. 2010;68:91–98.
http://www.ncbi.nlm.nih.gov/pubmed/20421843

62. Sanyanusin P, McNoe LA, Sullivan MJ, et al. Mutation of PAX2 in two siblings with renal-coloboma syndrome. Hum Mol Genet. 1995;4:2183–2184.
http://www.ncbi.nlm.nih.gov/pubmed/8589702

63. Quinlan J, Lemire M, Hudson T, et al. A common variant of the PAX2 gene is associated with reduced newborn kidney size. J Am Soc Nephrol. 2007;18:1915–1921.

64. Zhang Z, Quinlan J, Hoy W, et al. A common RET variant is associated with reduced newborn kidney size and function. J Am Soc Nephrol. 2008;19:2027–2034.

65. Zhang Z, Quinlan J, Grote D, et al. Common variants of the glial cell-derived neurotrophic factor gene do not influence kidney size of the healthy newborn. Pediatr Nephrol. 2009;24:1151–1157.

66. Hinchliffe SA, Howard CV, Lynch MR, et al. Renal developmental arrest in sudden infant death syndrome. Pediatr Pathol. 1993;13:333–343.
http://www.ncbi.nlm.nih.gov/pubmed/8516228

67. Gubhaju L, Sutherland MR, Yoder BA, et al. Is nephrogenesis affected by preterm birth? Studies in a non-human primate model. Am J Physiol Renal Physiol. 2009;297:F1668–F1677.

68. Hinchliffe SA, Lynch MR, Sargent PH, et al. The effect of intrauterine growth retardation on the development of renal nephrons. Br J Obstet Gynaecol. 1992;99:296–301.
http://www.ncbi.nlm.nih.gov/pubmed/1581274

69. Hinchliffe SA, Sargent PH, Howard CV, et al. Human intrauterine renal growth expressed in absolute number of glomeruli assessed by the disector method and Cavalieri principle. Lab Invest. 1991;64:777–784.
http://www.ncbi.nlm.nih.gov/pubmed/2046329

70. Hoy WE, Bertram JF, Denton RD, et al. Nephron number, glomerular volume, renal disease and hypertension. Curr Opin Nephrol Hypertens. 2008;17:258– 265.
http://www.ncbi.nlm.nih.gov/pubmed/18408476

71. Gilbert JS, Nijland MJ. Sex differences in the developmental origins of hypertension and cardiorenal disease. Am J Physiol Regul Integr Comp Physiol. 2008;295:R1941–1952.

72. Moritz KM, Cuffe JS, Wilson LB, et al. Review: Sex specific programming: a critical role for the renal renin-angiotensin system. Placenta. 2010;31 Suppl:S40– S46.

73. Li S, Chen SC, Shlipak M, et al. Low birth weight is associated with chronic kidney disease only in men. Kidney Int. 2008;73:637–642.
http://www.ncbi.nlm.nih.gov/pubmed/18094674

74. Hughson MD, Douglas-Denton R, Bertram JF, et al. Hypertension, glomerular number, and birth weight in African Americans and white subjects in the southeastern United States. Kidney Int. 2006;69:671–678.
http://www.ncbi.nlm.nih.gov/pubmed/16395270

75. McNamara BJ, Diouf B, Douglas-Denton RN, et al. A comparison of nephron number, glomerular volume and kidney weight in Senegalese Africans and African Americans. Nephrol Dial Transplant. 2010;25:1514–1520.

76. Collins JW, Rankin KM, David RJ. Low birth weight across generations: the effect of economic environment. Matern Child Health J. 2011;15(4):438–445.
http://www.ncbi.nlm.nih.gov/pubmed/20390329

77. Horta BL, Gigante DP, Osmond C, et al. Intergenerational effect of weight gain in childhood on offspring birthweight. Int J Epidemiol. 2009;38:724–732.
http://www.ncbi.nlm.nih.gov/pubmed/19376883

78. Vikse BE, Irgens LM, Bostad L, et al. Adverse perinatal outcome and later kidney biopsy in the mother. J Am Soc Nephrol. 2006;17:837–845.
http://www.ncbi.nlm.nih.gov/pubmed/16421228

79. Munkhaugen J, Lydersen S, Romundstad PR, et al. Kidney function and future risk for adverse pregnancy outcomes: a population-based study from HUNT II, Norway. Nephrol Dial Transplant. 2009;24(12):3744–3750.

80. Harrison M, Langley-Evans SC. Intergenerational programming of impaired nephrogenesis and hypertension in rats following maternal protein restriction during pregnancy. Br J Nutr. 2009;101:1020–1030.

81. Wlodek ME, Mibus A, Tan A, et al. Normal lactational environment restores nephron endowment and prevents hypertension after placental restriction in the rat. J Am Soc Nephrol. 2007;18:1688–1696.

82. Makrakis J, Zimanyi MA, Black MJ. Retinoic acid enhances nephron endowment in rats exposed to maternal protein restriction. Pediatr Nephrol. 2007;22:1861–1867.
http://www.ncbi.nlm.nih.gov/pubmed/17849154

83. El Kares R, Manolescu DC, Lakhal-Chaieb L, et al. A human ALDH1A2 gene variant is associated with increased newborn kidney size and serum retinoic acid. Kidney Int. 2010;78:96–102.
http://www.ncbi.nlm.nih.gov/pubmed/20375987

84. Li J, Khodus G, Kruusmagi M, et al. Ouabain protects against adverse developmental programming of the kidney. Nat Commun. 2010;1:42.
http://www.ncbi.nlm.nih.gov/pubmed/20975704

85. Vasarhelyi B, Dobos M, Reusz GS, et al. Normal kidney function and elevated natriuresis in young men born with low birth weight. Pediatr Nephrol. 2000;15:96–100.
http://www.ncbi.nlm.nih.gov/pubmed/11095022

86. Li J, Khodus GR, Kruusmagi M, et al. Ouabain protects against adverse developmental programming of the kidney. Nat Commun. 2010;1:1–7.
http://www.ncbi.nlm.nih.gov/pubmed/20975704

87. Mansano R, Desai M, Garg A, et al. Enhanced nephrogenesis in offspring of water-restricted rat dams. Am J Obstet Gynecol. 2007;196:480e1–6.
http://www.ncbi.nlm.nih.gov/pubmed/17466712

88. Okada T, Yamagishi T, Morikawa Y. Morphometry of the kidney in rat pups from uninephrectomized mothers. Anat Rec. 1994;240:120–124.
http://www.ncbi.nlm.nih.gov/pubmed/7810908

89. Averbukh Z, Bogin E, Cohn M, et al. The renotrophic factor, a persistent stimulus that crosses the placenta in mice. J Physiol. 1988;404:31–38.
http://www.ncbi.nlm.nih.gov/pubmed/3253434

90. Fulladosa X, Moreso F, Narvaez JA, et al. Estimation of total glomerular number in stable renal transplants. J Am Soc Nephrol. 2003;14:2662–2668.

91. Yiu V, Buka S, Zurakowski D, et al. Relationship between birthweight and blood pressure in childhood. Am J Kidney Dis. 1999;33:253–260.
http://www.ncbi.nlm.nih.gov/pubmed/10023635
92. Blumenshine P, Egerter S, Barclay CJ, et al. Socioeconomic disparities in adverse birth outcomes: a systematic review. Am J Prev Med. 2010;39:263–272.
http://www.ncbi.nlm.nih.gov/pubmed/20709259
93. Surkan PJ, Hsieh CC, Johansson AL, et al. Reasons for increasing trends in large for gestational age births. Obstet Gynecol. 2004;104:720–726.
http://www.ncbi.nlm.nih.gov/pubmed/15458892
94. Nelson RG, Morgenstern H, Bennett PH. Birth weight and renal disease in Pima Indians with type 2 diabetes mellitus. Am J Epidemiol. 1998;148:650–656.
http://www.ncbi.nlm.nih.gov/pubmed/9778171
95. Nelson RG, Morgenstern H, Bennett PH. Intrauterine diabetes exposure and the risk of renal disease in diabetic Pima Indians. Diabetes. 1998;47: 1489–1493.
96. Gilbert JS, Lang AL, Grant AR, et al. Maternal nutrient restriction in sheep: hypertension and decreased nephron number in offspring at 9 months of age. J Physiol. 2005;565:137–147.
http://www.ncbi.nlm.nih.gov/pubmed/15790663
97. Jones SE, Nyengaard JR, Flyvbjerg A, et al. Birth weight has no influence on glomerular number and volume. Pediatr Nephrol. 2001;16:340–345.
http://www.ncbi.nlm.nih.gov/pubmed/11354778
98. Hoy WE, Hughson MD, Singh GR, et al. Reduced nephron number and glomerulomegaly in Australian Aborigines: a group at high risk for renal disease and hypertension. Kidney Int. 2006;70:104–110.
http://www.ncbi.nlm.nih.gov/pubmed/16723986
99. Deutinger J, Bartl W, Pfersmann C, et al. Fetal kidney volume and urine production in cases of fetal growth retardation. J Perinat Med. 1987;15:307–315.
http://www.ncbi.nlm.nih.gov/pubmed/3323459
100. Kurjak A, Kirkinen P, Latin V, et al. Ultrasonic assessment of fetal kidney function in normal and complicated pregnancies. AmJ Obstet Gynecol. 1981;141:266–270.
101. Silver LE, Decamps PJ, Korst LM, et al. Intrauterine growth restriction is accompanied by decreased renal volume in the human fetus. Am J Obstet Gynecol. 2003;188:1320–1325.
102. Konje JC, Bell SC, Morton JJ, et al. Human fetal kidney morphometry during gestation and the relationship between weight, kidney morphometry and plasma active renin concentration at birth. Clin Sci (Lond). 1996;91:169–175.
103. Schmidt IM, Damgaard IN, Boisen KA, et al. Increased kidney growth in formula-fed versus breast-fed healthy infants. Pediatr Nephrol. 2004;19: 1137–1144.
http://www.ncbi.nlm.nih.gov/pubmed/15309602
104. Spencer J, Wang Z, Hoy W. Low birth weight and reduced renal volume in Aboriginal children. Am J Kidney Dis. 2001;37:915–920.
http://www.ncbi.nlm.nih.gov/pubmed/11325672
105. Simonetti GD, Raio L, Surbek D, et al. Salt sensitivity of children with low birth weight. Hypertension. 2008;52:625–630.
http://www.ncbi.nlm.nih.gov/pubmed/18695145
106. Rakow A, Johansson S, Legnevall L, et al. Renal volume and function in school-age children born preterm or small for gestational age. Pediatr Nephrol. 2008;23:1309–1315.
http://www.ncbi.nlm.nih.gov/pubmed/18491148
107. Keijzer-Veen MG, Dulger A, Dekker FW, et al. Very preterm birth is a risk factor for increased systolic blood pressure at a young adult age. Pediatr Nephrol. 2010;25:509–516.
http://www.ncbi.nlm.nih.gov/pubmed/20012998
108. Kent AL, Jyoti R, Robertson C, et al. Are renal volumes measured by magnetic resonance imaging and three-dimensional ultrasound in the term neonate comparable? Pediatr Nephrol. 2010;25:913–918.
109. Brenner BM, Mackenzie HS. Nephron mass as a risk factor for progression of renal disease. Kidney Int. Suppl 1997;63:S124–127.
110. Tan JC, Workeneh B, Busque S, et al. Glomerular function, structure, and number in renal allografts from older deceased donors. J Am Soc Nephrol. 2009; 20:181–188.
http://www.ncbi.nlm.nih.gov/pubmed/18815243
111. McNamara BJ, Diouf B, Hughson MD, et al. Associations between age, body size and nephron number with individual glomerular volumes in urban West African males. Nephrol Dial Transplant. 2009;24:1500–1506.
http://www.ncbi.nlm.nih.gov/pubmed/19028752
112. Hoy WE, Hughson MD, Zimanyi M, et al. Distribution of volumes of individual glomeruli in kidneys at autopsy: association with age, nephron number, birth weight and body mass index. Clin Nephrol. 2010;74:105–112.
113. Zimanyi MA, Hoy WE, Douglas-Denton RN, et al. Nephron number and individual glomerular volumes in male Caucasian and African American subjects. Nephrol Dial Transplant. 2009;24:2428–2433.
http://www.ncbi.nlm.nih.gov/pubmed/19297355
114. Ritz E, Koleganova N. African Americans compared to Senegalese—same number of glomeruli, but greater glomerular size. What does this tell us? Nephrol Dial Transplant. 2010;25:1368–1370.
http://www.ncbi.nlm.nih.gov/pubmed/20228072
115. Abdi R, Slakey D, Kittur D, et al. Baseline glomerular size as a predictor of function in human renal transplantation. Transplantation. 1998;66:329–333.
http://www.ncbi.nlm.nih.gov/pubmed/9721801
116. Hughson MD, Gobe GC, Hoy WE, et al. Associations of glomerular number and birth weight with clinicopathological features of African Americans and whites. Am J Kidney Dis. 2008;52:18–28.
http://www.ncbi.nlm.nih.gov/pubmed/18514988
117. Hodgin JB, Rasoulpour M, Markowitz GS, et al. Very low birth weight is a risk factor for secondary focal segmental glomerulosclerosis. Clin J Am Soc Nephrol. 2009;4:71–76.
http://www.ncbi.nlm.nih.gov/pubmed/21137017
118. Villar-Martini VC, Carvalho JJ, Neves MF, et al. Hypertension and kidney alterations in rat offspring from low protein pregnancies. J Hypertens Suppl. 2009;27:S47–51.
119. Benz K, Campean V, Cordasic N, et al. Early glomerular alterations in genetically determined low nephron number. Am J Physiol Renal Physiol. 2011;300(2):F521–530.
120. Jones SE, White KE, Flyvbjerg A, et al. The effect of intrauterine environment and low glomerular number on the histological changes in diabetic glomerulosclerosis. Diabetologia. 2006;49:191–199.
http://www.ncbi.nlm.nih.gov/pubmed/16365725
121. Barker DJ. The fetal origins of adult hypertension. J Hypertens Suppl. 1992;10:S39–44.
122. Curhan GC, Willett WC, Rimm EB, et al. Birth weight and adult hypertension, diabetes mellitus, and obesity in US men. Circulation. 1996;94:3246–3250.
http://www.ncbi.nlm.nih.gov/pubmed/8989136
123. Doyle LW, Faber B, Callanan C, et al. Blood pressure in late adolescence and very low birth weight. Pediatrics. 2003;111:252–257.
http://www.ncbi.nlm.nih.gov/pubmed/12563047
124. Langley SC, Jackson AA. Increased systolic blood pressure in adult rats induced by fetal exposure to maternal low protein diets. Clin Sci (Lond). 1994;86:217–222; discussion 121.
http://www.ncbi.nlm.nih.gov/pubmed/8143432
125. Longo-Mbenza B, Ngiyulu R, Bayekula M, et al. Low birth weight and risk of hypertension in African school children. J Cardiovasc Risk. 1999;6:311–314.
126. Manning J, Vehaskari VM. Low birth weight-associated adult hypertension in the rat. Pediatr Nephrol. 2001;16:417–422.
http://www.ncbi.nlm.nih.gov/pubmed/11405116
127. Huxley RR, Shiell AW, Law CM. The role of size at birth and postnatal catch-up growth in determining systolic blood pressure: a systematic review of the literature. J Hypertens. 2000;18:815–831.
http://www.ncbi.nlm.nih.gov/pubmed/10930178
128. Chen W Srinivasan SR, Berenson GS. Amplification of the association between birthweight and blood pressure with age: the Bogalusa Heart Study. J Hypertens. 2010;28:2046–2052.
http://www.ncbi.nlm.nih.gov/pubmed/20616754
129. Vancheri F, Alletto M, Burgio A, et al. [Inverse relationship between fetal growth and arterial pressure in children and adults]. G Ital Cardiol. 1995;25: 833–841.
http://www.ncbi.nlm.nih.gov/pubmed/7557032
130. Yang S, Bergvall N, Cnattingius S, et al. Gestational age differences in health and development among young Swedish men born at term. Int J Epidemiol. 2010;39:1240–1249.
http://www.ncbi.nlm.nih.gov/pubmed/20483833
131. Keijzer-Veen MG, Schrevel M, Finken MJ, et al. Microalbuminuria and lower glomerular filtration rate at young adult age in subjects born very premature and after intrauterine growth retardation. J Am Soc Nephrol. 2005;16: 2762–2768.
http://www.ncbi.nlm.nih.gov/pubmed/15987756
132. Schmidt IM, Chellakooty M, Boisen KA, et al. Impaired kidney growth in low-birth-weight children: distinct effects of maturity and weight for gestational age. Kidney Int. 2005;68:731–740.
http://www.ncbi.nlm.nih.gov/pubmed/16014050
133. Siewert-Delle A, Ljungman S. The impact of birth weight and gestational age on blood pressure in adult life: a population-based study of 49-year-old men. Am J Hypertens. 1998;11:946–953.
134. Wen X, Triche EW, Hogan JW, et al. Association between placental morphology and childhood systolic blood pressure. Hypertension. 2011;57: 48–55.
http://www.ncbi.nlm.nih.gov/pubmed/21079045

135. Bergvall N, Iliadou A, Johansson S, et al. Genetic and shared environmental factors do not confound the association between birth weight and hypertension: a study among Swedish twins. Circulation. 2007;115:2931–2938.
http://www.ncbi.nlm.nih.gov/pubmed/17515462
136. Levine RS, Hennekens CH, Jesse MJ. Blood pressure in prospective population based cohort of newborn and infant twins. Br Med J. 1994;308:298–302.
137. Chen W, Srinivasan SR, Hallman DM, et al. The relationship between birthweight and longitudinal changes of blood pressure is modulated by beta-adrenergic receptor genes: the Bogalusa Heart Study. J Biomed Biotechnol. 2010;2010:543514.
http://www.ncbi.nlm.nih.gov/pubmed/20467565
138. Falkner B, Hulman S, Kushner H. Effect of birth weight on blood pressure and body size in early adolescence. Hypertension. 2004;43:203–207.
http://www.ncbi.nlm.nih.gov/pubmed/14676220
139. Huxley R, Neil A, Collins R. Unravelling the fetal origins hypothesis: is there really an inverse association between birthweight and subsequent blood pressure? Lancet. 2002;360:659–665.
http://www.ncbi.nlm.nih.gov/pubmed/12241871
140. Muhle A, Muhle C, Amann K, et al. No juvenile arterial hypertension in sheep multiples despite reduced nephron numbers. Pediatr Nephrol. 2010;25:1653–1661.
http://www.ncbi.nlm.nih.gov/pubmed/20386927
141. Rostand SG, Cliver SP, Goldenberg RL. Racial disparities in the association of foetal growth retardation to childhood blood pressure. Nephrol Dial Transplant. 2005;20:1592–1597.
http://www.ncbi.nlm.nih.gov/pubmed/15840672
142. McCormick Covelli M. The relationship of low birth weight to blood pressure, cortisol levels, and reactivity in African American adolescents: a pilot study. Issues Compr Pediatr Nurs. 2006;29:173–187.
http://www.ncbi.nlm.nih.gov/pubmed/16923680
143. Forrester T. Historic and early life origins of hypertension in Africans. J Nutr. 2004;134:211–216.
http://www.ncbi.nlm.nih.gov/pubmed/14704321
144. Hemachandra AH, Klebanoff MA, Furth SL. Racial disparities in the association between birth weight in the term infant and blood pressure at age 7 years: results from the collaborative perinatal project. J Am Soc Nephrol. 2006;17:2576–2581.
http://www.ncbi.nlm.nih.gov/pubmed/16870709
145. Levitt NS, Steyn K, De Wet T, et al. An inverse relation between blood pressure and birth weight among 5 year old children from Soweto, South Africa. J Epidemiol Community Health. 1999;53:264–268.
http://www.ncbi.nlm.nih.gov/pubmed/10396531
146. Gilbert T, Lelievre-Pegorier M, Merlet-Benichou C. Long-term effects of mild oligonephronia induced in utero by gentamicin in the rat. Pediatr Res. 1991;30:450–456.
http://www.ncbi.nlm.nih.gov/pubmed/1754301
147. Langley-Evans SC. Intrauterine programming of hypertension in the rat: nutrient interactions. Comp Biochem Physiol A Physiol. 1996;114:327–333.
http://www.ncbi.nlm.nih.gov/pubmed/8759281
148. Ortiz LA, Quan A, Weinberg A, et al. Effect of prenatal dexamethasone on rat renal development. Kidney Int. 2001;59:1663–1669.
http://www.ncbi.nlm.nih.gov/pubmed/11318936
149. Woods LL, Ingelfinger JR, Nyengaard JR, et al. Maternal protein restriction suppresses the newborn renin-angiotensin system and programs adult hypertension in rats. Pediatr Res. 2001;49:460–467.
http://www.ncbi.nlm.nih.gov/pubmed/11264427
150. Alexander BT. Placental insufficiency leads to development of hypertension in growth-restricted offspring. Hypertension. 2003;41:457–462.
http://www.ncbi.nlm.nih.gov/pubmed/12623943
151. Langley-Evans SC, Jackson AA. Rats with hypertension induced by in utero exposure to maternal low-protein diets fail to increase blood pressure in response to a high salt intake. Ann Nutr Metab. 1996;40:1–9.
152. Boubred F, Buffat C, Feuerstein JM, et al. Effects of early postnatal hypernutrition on nephron number and long-term renal function and structure in rats. Am J Physiol Renal Physiol. 2007;293:F1944–1949.
153. Ibrahim HN, Foley R, Tan L, et al. Long-term consequences of kidney donation. N Engl J Med. 2009;360:459–469.
http://www.ncbi.nlm.nih.gov/pubmed/19179315
154. Kett MM, Bertram JF. Nephron endowment and blood pressure: what do we really know? Curr Hypertens Rep. 2004;6:133–139.
http://www.ncbi.nlm.nih.gov/pubmed/15010018
155. Moritz KM, Wintour EM, Dodic M. Fetal uninephrectomy leads to postnatal hypertension and compromised renal function. Hypertension. 2002;39:1071–1076.
http://www.ncbi.nlm.nih.gov/pubmed/12052844
156. Singh RR, Denton KM, Bertram JF, et al. Development of cardiovascular disease due to renal insufficiency in male sheep following fetal unilateral nephrectomy. J Hypertens. 2009;27:386–396.
http://www.ncbi.nlm.nih.gov/pubmed/19155792
157. Woods LL, Weeks DA, Rasch R. Hypertension after neonatal uninephrectomy in rats precedes glomerular damage. Hypertension. 2001;38:337–342.
http://www.ncbi.nlm.nih.gov/pubmed/11566901
158. Nyengaard JR. Number and dimensions of rat glomerular capillaries in normal development and after nephrectomy. Kidney Int. 1993;43:1049–1057.
159. Gibney EM, Parikh CR, Garg AX. Age, gender, race, and associations with kidney failure following living kidney donation. Transplant Proc. 2008;40:1337–1340.
160. Abdi R, Slakey D, Kittur D, et al. Heterogeneity of glomerular size in normal donor kidneys: Impact of race. Am J Kidney Dis. 1998;32:43–46.
http://www.ncbi.nlm.nih.gov/pubmed/10407369
161. Baum M. Overview of chronic kidney disease in children. Curr Opin Pediatr. 2010;22:158–160.
http://www.ncbi.nlm.nih.gov/pubmed/20299869
162. Luyckx VA, Brenner BM. The clinical importance of nephron mass. J Am Soc Nephrol. 2010;21:898–910.
http://www.ncbi.nlm.nih.gov/pubmed/20150537
163. Ligi I, Grandvuillemin I, Andres V, et al. Low birth weight infants and the developmental programming of hypertension: a focus on vascular factors. Semin Perinatol. 2010;34:188–192.
http://www.ncbi.nlm.nih.gov/pubmed/20494734
164. Nuyt AM. Mechanisms underlying developmental programming of elevated blood pressure and vascular dysfunction: evidence from human studies and experimental animal models. Clin Sci (Lond). 2008;114:1–17.
165. Franco MC, Christofalo DM, Sawaya AL, et al. Effects of low birth weight in 8- to 13-year-old children: implications in endothelial function and uric acid levels. Hypertension. 2006;48:45–50.
http://www.ncbi.nlm.nih.gov/pubmed/17913201
166. Vehaskari VM. Programming of hypertension: the nervous kidney. Am J Physiol Renal Physiol. 2008;295:F27–28.
167. Dodic M, Moritz K, Koukoulas I, et al. Programmed hypertension: kidney, brain or both? Trends Endocrinol Metab. 2002;13:403–408.
http://www.ncbi.nlm.nih.gov/pubmed/12367823
168. Nehiri T, Duong Van Huyen JP, Viltard M, et al. Exposure to maternal diabetes induces salt-sensitive hypertension and impairs renal function in adult rat offspring. Diabetes. 2008;57:2167–2175.
http://www.ncbi.nlm.nih.gov/pubmed/18443204
169. Sanders MW, Fazzi GE, Janssen GM, et al. High sodium intake increases blood pressure and alters renal function in intrauterine growth-retarded rats. Hypertension. 2005;46:71–75.
http://www.ncbi.nlm.nih.gov/pubmed/15956110
170. Zimanyi MA, Bertram JF, Black MJ. Does a nephron deficit in rats predispose to salt-sensitive hypertension? Kidney Blood Press Res. 2004;27:239–247.
http://www.ncbi.nlm.nih.gov/pubmed/15273426
171. Gilbert JS. Sex, salt, and senescence: sorting out mechanisms of the developmental origins of hypertension. Hypertension. 2008;51:997–999.
http://www.ncbi.nlm.nih.gov/pubmed/18259036
172. Salazar F, Reverte V, Saez F, et al. Age- and sodium-sensitive hypertension and sex-dependent renal changes in rats with a reduced nephron number. Hypertension. 2008;51:1184–1189.
http://www.ncbi.nlm.nih.gov/pubmed/18259039
173. Magalhaes JC, da Silveira AB, Mota DL, et al. Renal function in juvenile rats subjected to prenatal malnutrition and chronic salt overload. Exp Physiol. 2006;91:611–619.
http://www.ncbi.nlm.nih.gov/pubmed/16513822
174. Stewart T, Ascani J, Craver RD, et al. Role of postnatal dietary sodium in prenatally programmed hypertension. Pediatr Nephrol. 2009;24:1727–1733.
175. Ruta LA, Dickinson H, Thomas MC, et al. High-salt diet reveals the hypertensive and renal effects of reduced nephron endowment. Am J Physiol Renal Physiol. 2010;298:F1384–1392.
176. de Boer MP, Ijzerman RG, de Jongh RT, et al. Birth weight relates to salt sensitivity of blood pressure in healthy adults. Hypertension. 2008;51:928–932.
http://www.ncbi.nlm.nih.gov/pubmed/18287343
177. Dagan A, Habib S, Gattineni J, et al. Prenatal programming of rat thick ascending limb chloride transport by low-protein diet and dexamethasone. Am J Physiol Regul Integr Comp Physiol. 2009;297:R93–99.
178. Manning J, Beutler K, Knepper MA, et al. Upregulation of renal BSC1 and TSC in prenatally programmed hypertension. Am J Physiol Renal Physiol. 2002;283:F202–206.

179. Dagan A, Kwon HM, Dwarakanath V, et al. Effect of renal denervation on prenatal programming of hypertension and renal tubular transporter abundance. Am J Physiol Renal Physiol. 2008;295:F29–34.
180. Bertram C, Trowern AR, Copin N, et al. The maternal diet during pregnancy programs altered expression of the glucocorticoid receptor and type 2 11beta-hydroxysteroid dehydrogenase: potential molecular mechanisms underlying the programming of hypertension in utero. Endocrinology. 2001;142:2841–2853.
181. Alwasel SH, Kaleem I, Sahajpal V, et al. Maternal protein restriction reduces angiotensin II AT(1) and AT(2) receptor expression in the fetal rat kidney. Kidney Blood Press Res. 2010;33:251–259.
http://www.ncbi.nlm.nih.gov/pubmed/20606474
182. Grigore D, Ojeda NB, Robertson EB, et al. Placental insufficiency results in temporal alterations in the renin angiotensin system in male hypertensive growth restricted offspring. Am J Physiol Regul Integr Comp Physiol. 2007;293:R804–811.
183. Manning J, Vehaskari VM. Postnatal modulation of prenatally programmed hypertension by dietary Na and ACE inhibition. Am J Physiol Regul Integr Comp Physiol. 2005;288:R80–84.
184. Cornock R, Langley-Evans SC, Mobasheri A, et al. The impact of maternal protein restriction during rat pregnancy upon renal expression of angiotensin receptors and vasopressin-related aquaporins. Reprod Biol Endocrinol. 2010;8:105.
http://www.ncbi.nlm.nih.gov/pubmed/20807409
185. Gwathmey TM, Shaltout HA, Rose JC, et al. Glucocorticoid-induced fetal programming alters the functional complement of angiotensin receptor subtypes within the kidney. Hypertension. 2011;57:620–626.
http://www.ncbi.nlm.nih.gov/pubmed/21220702
186. Barker DJ, Osmond C, Forsen TJ, et al. Trajectories of growth among children who have coronary events as adults. N Engl J Med. 2005;353:1802–1809.
http://www.ncbi.nlm.nih.gov/pubmed/16251536
187. Boubred F, Daniel L, Buffat C, et al. Early postnatal overfeeding induces early chronic renal dysfunction in adult male rats. Am J Physiol Renal Physiol. 2009;297:F943–951.
188. Fainberg HP, Budge H, Symonds ME. The conflicting effects of maternal nutrient restriction and early-life obesity on renal health. Proc Nutr Soc. 2011: 1–8.
http://www.ncbi.nlm.nih.gov/pubmed/21232171
189. Singhal A, Cole TJ, Fewtrell M, et al. Is slower early growth beneficial for long-term cardiovascular health? Circulation. 2004;109:1108–1113.
http://www.ncbi.nlm.nih.gov/pubmed/14993136
190. Ben-Shlomo Y, McCarthy A, Hughes R, et al. Immediate postnatal growth is associated with blood pressure in young adulthood: the Barry Caerphilly Growth Study. Hypertension. 2008;52:638–644.
http://www.ncbi.nlm.nih.gov/pubmed/18768401
191. Hemachandra AH, Howards PP, Furth SL, et al. Birth weight, postnatal growth, and risk for high blood pressure at 7 years of age: results from the Collaborative Perinatal Project. Pediatrics. 2007;119:e1264–1270.
192. Law CM, Shiell AW, Newsome CA, et al. Fetal, infant, and childhood growth and adult blood pressure: a longitudinal study from birth to 22 years of age. Circulation. 2002;105:1088–1092.
193. Luyckx VA, Compston CA, Simmen T, et al. Accelerated senescence in kidneys of low-birth-weight rats after catch-up growth. Am J Physiol Renal Physiol. 2009;297:F1697–1705.
194. Ozanne SE, Hales CN. Lifespan: catch-up growth and obesity in male mice. Nature. 2004;427:411–412.
http://www.ncbi.nlm.nih.gov/pubmed/14749819
195. Tarry-Adkins JL, Martin-Gronert MS, Chen JH, et al. Maternal diet influences DNA damage, aortic telomere length, oxidative stress, and antioxidant defense capacity in rats. FASEBJ. 2008;22:2037–2044.
http://www.ncbi.nlm.nih.gov/pubmed/14749819
196. Tarry-Adkins JL, Ozanne SE, Norden A, et al. Lower antioxidant capacity and elevated p53 and p21 may be a link between gender disparity in renal telomere shortening, albuminuria, and longevity. Am J Physiol Renal Physiol. 2006;290:F509–516.
197. Akkad A, Hastings R, Konje JC, et al. Telomere length in small-for- gestational-age babies. BJOG. 2006;113:318–323.
http://www.ncbi.nlm.nih.gov/pubmed/16487204
198. Raqib R, Alam DS, Sarker P, et al. Low birth weight is associated with altered immune function in rural Bangladeshi children: a birth cohort study. Am J Clin Nutr. 2007;85:845–852.
http://www.ncbi.nlm.nih.gov/pubmed/17344508
199. Mohn A, Chiavaroli V, Cerruto M, et al. Increased oxidative stress in prepubertal children born small for gestational age. J Clin Endocrinol Metab. 2007;92:1372–1378.
http://www.ncbi.nlm.nih.gov/pubmed/17264184
200. Franco MC, Kawamoto EM, Gorjao R, et al. Biomarkers of oxidative stress and antioxidant status in children born small for gestational age: evidence of lipid peroxidation. Pediatr Res. 2007;62:204–208.
http://www.ncbi.nlm.nih.gov/pubmed/17597662
201. Schreuder MF, Wilhelm AJ, Bokenkamp A, et al. Impact of gestational age and birth weight on amikacin clearance on day 1 of life. Clin J Am Soc Nephrol. 2009;4:1774–1778.
http://www.ncbi.nlm.nih.gov/pubmed/19713296
202. Bauer R, Walter B, Bauer K, et al. Intrauterine growth restriction reduces nephron number and renal excretory function in newborn piglets. Acta Physiol Scand. 2002;176:83–90.
http://www.ncbi.nlm.nih.gov/pubmed/12354166
203. Rodriguez-Soriano J, Aguirre M, Oliveros R, et al. Long-term renal follow-up of extremely low birth weight infants. Pediatr Nephrol. 2005;20:579–584.
http://www.ncbi.nlm.nih.gov/pubmed/15782301
204. Franco MC, Nishida SK, Sesso R. GFR estimated from cystatin C versus creatinine in children born small for gestational age. Am J Kidney Dis. 2008;51:925–932.
http://www.ncbi.nlm.nih.gov/pubmed/18455848
205. Gielen M, Pinto-Sietsma SJ, Zeegers MP, et al. Birth weight and creatinine clearance in young adult twins: influence of genetic, prenatal, and maternal factors. J Am Soc Nephrol. 2005;16:2471–2476.
http://www.ncbi.nlm.nih.gov/pubmed/15944342
206. Hallan S, Euser AM, Irgens LM, et al. Effect of intrauterine growth restriction on kidney function at young adult age: the Nord Trondelag Health (HUNT 2) Study. Am J Kidney Dis. 2008;51:10–20.
http://www.ncbi.nlm.nih.gov/pubmed/18155528
207. White SL, Perkovic V, Cass A, et al. Is low birth weight an antecedent of CKD in later life? A systematic review of observational studies. Am J Kidney Dis. 2009;54:248–261.
http://www.ncbi.nlm.nih.gov/pubmed/19339091
208. Keijzer-Veen MG, Kleinveld HA, Lequin MH, et al. Renal function and size at young adult age after intrauterine growth restriction and very premature birth. Am J Kidney Dis. 2007;50:542–551.
http://www.ncbi.nlm.nih.gov/pubmed/17900453
209. Salgado CM, Jardim PC, Teles FB, et al. Influence of low birth weight on microalbuminuria and blood pressure of school children. Clin Nephrol. 2009;71:367–374.
http://www.ncbi.nlm.nih.gov/pubmed/19356368
210. Hoy WE, Wang Z, VanBuynder P, et al. The natural history of renal disease in Australian Aborigines. Part 2. Albuminuria predicts natural death and renal failure. Kidney Int. 2001;60:249–256.
http://www.ncbi.nlm.nih.gov/pubmed/11422758
211. Yudkin JS, Martyn CN, Phillips DI, et al. Associations of micro-albuminuria with intra-uterine growth retardation. Nephron. 2001;89:309–314.
http://www.ncbi.nlm.nih.gov/pubmed/11598395
212. Hoy WE, Mathews JD, McCredie DA, et al. The multidimensional nature of renal disease: rates and associations of albuminuria in an Australian Aboriginal community. Kidney Int. 1998;54:1296–1304.
http://www.ncbi.nlm.nih.gov/pubmed/9767547
213. Hoy WE, Wang Z, VanBuynder P, et al. The natural history of renal disease in Australian Aborigines. Part 1. Changes in albuminuria and glomerular filtration rate over time. Kidney Int. 2001;60:243–248.
http://www.ncbi.nlm.nih.gov/pubmed/11422757
214. Fagerudd J, Forsblom C, Pettersson-Fernholm K, et al. Low birth weight does not increase the risk of nephropathy in Finnish type 1 diabetic patients. Nephrol Dial Transplant. 2006;21:2159–2165.
215. Rossing P, Tarnow L, Nielsen FS, et al. Low birth weight. A risk factor for development of diabetic nephropathy? Diabetes. 1995;44:1405–1407.
http://www.ncbi.nlm.nih.gov/pubmed/7589846
216. Rossing P, Tarnow L, Nielsen FS, et al. Short stature and diabetic nephropa- thy. Br Med J. 1995;310:296–297.
http://www.ncbi.nlm.nih.gov/pubmed/7866171
217. Vikse BE, Irgens LM, Leivestad T, et al. Low birth weight increases risk for end-stage renal disease. J Am Soc Nephrol. 2008;19:151–157.
http://www.ncbi.nlm.nih.gov/pubmed/18057216
218. Lackland DT, Bendall HE, Osmond C, et al. Low birth weights contribute to high rates of early-onset chronic renal failure in the Southeastern United States. Arch Intern Med. 2000;160:1472–1476.
219. Duncan RC, Bass PS, Garrett PJ, et al. Weight at birth and other factors influencing progression of idiopathic membranous nephropathy. Nephrol Dial Transplant. 1994;9(7):875.
220. Na YW, Yang HJ, Choi JH, et al. Effect of intrauterine growth retardation on the progression of nephrotic syndrome. Am J Nephrol. 2002;22:463–467.
http://www.ncbi.nlm.nih.gov/pubmed/12381944

221. Teeninga N, Schreuder MF, Bokenkamp A, et al. Influence of low birth weight on minimal change nephrotic syndrome in children, including a meta-analysis. Nephrol Dial Transplant. 2008;23:1615–1620.
http://www.ncbi.nlm.nih.gov/pubmed/18065792
222. Zidar N, Cavic MA, Kenda RB, et al. Effect of intrauterine growth retardation on the clinical course and prognosis of IgA glomerulonephritis in children. Nephron. 1998;79:28–32.
http://www.ncbi.nlm.nih.gov/pubmed/9609458
223. Jones SE, Bilous RW, Flyvbjerg A, et al. Intra-uterine environment influences glomerular number and the acute renal adaptation to experimental diabetes. Diabetologia. 2001;44:721–728.
224. Plank C, Nusken KD, Menendez-Castro C, et al. Intrauterine growth restriction following ligation of the uterine arteries leads to more severe glomerulosclerosis after mesangioproliferative glomerulonephritis in the offspring. Am J Nephrol. 2010;32:287–295.
http://www.ncbi.nlm.nih.gov/pubmed/20714134
225. Hakim RM, Goldszer RC, Brenner BM. Hypertension and proteinuria: long-term sequelae of uninephrectomy in humans. Kidney Int. 1984;25:930–936.
http://www.ncbi.nlm.nih.gov/pubmed/6381857
226. Rogers NM, Lawton PD, Jose MD. Indigenous Australians and living kidney donation. N Engl J Med. 2009;361:1513–1516.
http://www.ncbi.nlm.nih.gov/pubmed/19812415
227. Storsley LJ, Young A, Rush DN, et al. Long-term medical outcomes among Aboriginal living kidney donors. Transplantation. 2010;90:401–406.
http://www.ncbi.nlm.nih.gov/pubmed/20562735
228. Lentine KL, Schnitzler MA, Xiao H, et al. Racial variation in medical outcomes among living kidney donors. N Engl J Med. 2010;363:724–732.
http://www.ncbi.nlm.nih.gov/pubmed/20818874
229. Brenner BM, Milford EL. Nephron underdosing: A programmed cause of chronic renal allograft failure. Am J Kidney Dis. 1993;21:66–72.
http://www.ncbi.nlm.nih.gov/pubmed/8494022
230. Szabo AJ, Muller V, Chen GF, et al. Nephron number determines susceptibility to renal mass reduction-induced CKD in Lewis and Fisher 344 rats: implications for development of experimentally induced chronic allograft nephropathy. Nephrol Dial Transplant. 2008;23:2492–2495.
231. Douverny JB, Baptista-Silva JC, Pestana JO, et al. Importance of renal mass on graft function outcome after 12 months of living donor kidney transplantation. Nephrol Dial Transplant. 2007;22:3646–3651.
http://www.ncbi.nlm.nih.gov/pubmed/17704114
232. el-Agroudy AE, Hassan NA, Bakr MA, et al. Effect of donor/recipient body weight mismatch on patient and graft outcome in living-donor kidney transplantation. Am J Nephrol. 2003;23:294–299.
http://www.ncbi.nlm.nih.gov/pubmed/12902614
233. Gaston RS, Hudson SL, Julian BA, et al. Impact of donor/recipient size matching on outcomes in renal transplantation. Transplantation. 1996;61:383–388.
234. Kasiske BL, Snyder JJ, Gilbertson D. Inadequate donor size in cadaver kidney transplantation. J Am Soc Nephrol. 2002;13:2152–2159.
http://www.ncbi.nlm.nih.gov/pubmed/12138149
235. Kim YS, Kim MS, Han DS, et al. Evidence that the ratio of donor kidney weight to recipient body weight, donor age, and episodes of acute rejection correlate independently with live-donor graft function. Transplantation. 2002;72:280–283.
http://www.ncbi.nlm.nih.gov/pubmed/12151743
236. Giral M, Nguyen JM, Karam G, et al. Impact of graft mass on the clinical outcome of kidney transplants. J Am Soc Nephrol. 2005;16:261–268.
http://www.ncbi.nlm.nih.gov/pubmed/15563571
237. Giral M, Foucher Y, Karam G, et al. Kidney and recipient weight incompatibility reduces long-term graft survival. J Am Soc Nephrol. 2010;21:1022–1029.
238. Kim YS, Moon JI, Kim DK, et al. Ratio of donor kidney weight to recipient bodyweight as an index of graft function. Lancet. 2001;357:1180–1181.
239. Nakatani T, Sugimura K, Kawashima H, et al. The influence of recipient body mass on the outcome of cadaver kidney transplants. Clin Exp Nephrol. 2002;6:158–162.
240. Doshi MD, Garg N, Reese PP, et al. Recipient risk factors associated with delayed graft function: a paired kidney analysis. Transplantation. 2011;91:666–671.
241. Nicholson ML, Windmill DC, Horsburgh T, et al. Influence of allograft size to recipient body-weight ratio on the long-term outcome of renal transplantation. Br J Surg. 2000;87:314–319.
http://www.ncbi.nlm.nih.gov/pubmed/10718800
242. Johansson S, Iliadou A, Bergvall N, et al. The association between low birth weight and type 2 diabetes: contribution of genetic factors. Epidemiology. 2008;19:659–665.
http://www.ncbi.nlm.nih.gov/pubmed/18714437
243. Tian JY, Cheng Q, Song XM, et al. Birth weight and risk of type 2 diabetes, abdominal obesity and hypertension among Chinese adults. Eur J Endocrinol. 2006;155:601–607.
http://www.ncbi.nlm.nih.gov/pubmed/16990660
244. Elmes MJ, McMullen S, Gardner DS, et al. Prenatal diet determines susceptibility to cardiac ischaemia-reperfusion injury following treatment with diethylmaleic acid and N-acetylcysteine. Life Sci. 2008;82:149–155.
http://www.ncbi.nlm.nih.gov/pubmed/18062993
245. Rothermund L, Lorenz M, Schnieber A, et al. Impact of nephron number dosing on cardiorenal damage and effects of ACE inhibition. Am J Hypertens. 2011;24(4):474–481.
http://www.ncbi.nlm.nih.gov/pubmed/20864942
246. Langley-Evans SC. Nutritional programming of disease: unravelling the mechanism. J Anat. 2009;215:36–51.
http://www.ncbi.nlm.nih.gov/pubmed/19175805
247. Amri K, Freund N, Van Huyen JP, et al. Altered nephrogenesis due to maternal diabetes is associated with increased expression of IGF-II/mannose-6-phosphate receptor in the fetal kidney. Diabetes. 2001;50:1069–1075.
248. Gilbert T, Cibert C, Moreau E, et al. Early defect in branching morphogenesis of the ureteric bud in induced nephron deficit. Kidney Int. 1996;50:783–795.
http://www.ncbi.nlm.nih.gov/pubmed/8872952
249. Schreuder M, Delemarre-van de Waal H, van Wijk A. Consequences of intrauterine growth restriction for the kidney. Kidney Blood Press Res. 2006;29:108–125
http://www.ncbi.nlm.nih.gov/pubmed/16837795.