

# The Clinical Importance of Nephron Mass

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## ABSTRACT

Abundant evidence supports the association between low birth weight (LBW) and renal dysfunction in humans. Anatomic measurements of infants, children, and adults show significant inverse correlation between LBW and nephron number. Nephron numbers are also lower in individuals with hypertension compared with normotension among white and Australian Aboriginal populations. The relationship between nephron number and hypertension among black individuals is still unclear, although the high incidence of LBW predicts low nephron number in this population as well. LBW, a surrogate for low nephron number, also associates with increasing BP from childhood to adulthood and increasing risk for chronic kidney disease in later life. Because nephron numbers can be counted only postmortem, surrogate markers such as birth weight, prematurity, adult height, reduced renal size, and glomerulomegaly are potentially useful for risk stratification, for example, during living-donor assessment. Because early postnatal growth also affects subsequent risk for higher BP or reduced renal function, postnatal nutrition, a potentially modifiable factor, in addition to intrauterine effects, has significant influence on long-term cardiovascular and renal health.

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Low birth weight (LBW; defined by the World Health Organization as a birth weight <2500 g, or <5.5 lb) and adult cardiovascular disease have long been associated with poor fetal growth.<sup>1–4</sup> Studies from diverse populations validate these findings and now include related disorders such as hypertension, type 2 diabetes, obesity, and chronic kidney disease (CKD).<sup>4–10</sup> Developmental programming is the term used to describe longitudinal structure–function effects that are experienced during critical periods of fetal and early postnatal growth in response to environmental stimuli.<sup>1,4</sup> Emerging data suggest developmental programming may be the first in a succession of intrauterine events that ultimately manifests as overt disease.

LBW results from either intrauter-

ine growth restriction (IUGR) or preterm birth. The incidence of LBW is increasing in developed countries, largely as a result of increasing preterm birth, and remains highly prevalent in poorer countries largely as a result of maternal malnutrition and infection. Consequences of LBW therefore remain relevant worldwide.<sup>11</sup> LBW associated with IUGR generally reflects intrauterine stress during late gestation as opposed to LBW of preterm birth, which may be an appropriate weight for the duration of gestation. Term LBW has the strongest association with adult disease.<sup>12</sup> Conversely, high birth weight (HBW) usually as a result of maternal gestational diabetes also associates with risk for adult disease. The prevalence of LBW is greater among black individuals and Aboriginal Aus-

tralians and HBW among Native American compared with white individuals, the former being populations with disproportionately high rates of hypertension, CKD, diabetes, and cardiovascular disease.<sup>13–17</sup> Here we review evidence for developmental programming in the kidney and its later life consequences.

## DEVELOPMENTAL PROGRAMMING IN THE KIDNEY

A number of parameters have been used to assess developmental programming in the kidney.

### Nephron Number

In 1988, Brenner *et al.*<sup>18</sup> proposed that congenital or programmed reduction in nephron number ( $N_{\text{glom}}$ ) explains why some individuals are susceptible to hypertension and renal injury whereas others with sodium excess or diabetes seem relatively resistant under similar circumstances. A reduction in  $N_{\text{glom}}$  and therefore whole-kidney glomerular surface area would result in reduced sodium excretory capacity, enhanced susceptibility to hypertension, and reduced renal reserve, thereby limiting compensation for

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renal injury and possibly explaining the higher prevalence of hypertension and renal disease observed in populations with high prevalence of LBW.<sup>16,19–21</sup> Multiple animal models demonstrated an association of LBW with subsequent hypertension, which is mediated, at least in part, by a congenital deficit in nephron number.<sup>22–30</sup> Low  $N_{\text{glom}}$  alone, however, does not account for all experimentally programmed hypertension, suggesting that factors in addition to or independent of  $N_{\text{glom}}$  also participate.<sup>31,32</sup> Experimental models of reduced  $N_{\text{glom}}$  are outlined in Table 1 and reviewed elsewhere.<sup>33–35</sup>

The difficulty of accurately counting nephrons is an obstacle to investigating the  $N_{\text{glom}}$  hypothesis.<sup>36</sup> From early studies, using techniques such as acid-maceration or traditional stereologic analysis, humans were believed to have an average of approximately 1 million nephrons per kidney but with considerable interin-

dividual variability.<sup>37</sup> These techniques, however, are prone to methodologic bias.<sup>36–38</sup> More recently, an unbiased fractionator-sampling/dissector-counting method was developed and is thought to be more reproducible and objective.<sup>36–39</sup> Using the fractionator technique, among 37 normal Danish adults, the average  $N_{\text{glom}}$  was 617,000 per kidney (range 331,000 to 1,424,000).<sup>37</sup> Kidney weight was also proportional to  $N_{\text{glom}}$ .<sup>37</sup> Another study of 78 kidneys from individuals of diverse origins found a similar mean of 784,909 glomeruli per kidney (range 210,332 to 1,825,380).<sup>40</sup> The median  $N_{\text{glom}}$  in 10 normal white individuals, however, was 1,429,200. The large variability of  $N_{\text{glom}}$  within these presumed normal populations might reflect true variability, small samples sizes, or caution about the reproducibility of the fractionator technique.<sup>37,41</sup> Within each study, however, kidneys were likely handled similarly and there-

fore comparisons between groups remain valid.

Despite the finding that  $N_{\text{glom}}$  varies widely in normal populations, most data strongly support a direct relationship between  $N_{\text{glom}}$  and birth weight.<sup>42–45</sup> Current human data on  $N_{\text{glom}}$  are summarized in Table 2. A regression coefficient derived from the linear relationship between  $N_{\text{glom}}$  and birth weight in 56 individuals including males, females, adults, children, and black and white individuals predicted an increase of 257,426 glomeruli per kilogram increase in birth weight.<sup>42</sup>  $N_{\text{glom}}$  declines with age in the normal population without renal disease, at a rate of approximately 4500 glomeruli per kidney per year.<sup>46</sup>  $N_{\text{glom}}$  also tends to be lower in female individuals.<sup>43</sup> Birth weight, age, and gender therefore add to the observed variability in  $N_{\text{glom}}$ .

In humans, kidney development begins during the ninth week of gestation and continues until the 34th through

**Table 1.** Experimental models and mechanisms of reduced nephron number

Experimental Model	Proposed Mechanism of Nephron Number Reduction	Reference
Maternal low-protein diet	↑ apoptosis in metanephros and postnatal kidney Altered gene expression in developing kidney Altered gene methylation	169–171
Maternal vitamin A restriction	↓ placental 11-βHSD2 expression ↓ branching of ureteric bud ? maintenance of spatial orientation of vascular development ↓ c-ret expression	172
Maternal iron restriction	? reduced oxygen delivery ? altered glucocorticoid responsiveness ? altered micronutrient availability	173
Gestational glucocorticoid exposure	↑ fetal glucocorticoid exposure ? enhanced tissue maturation ↑ glucocorticoid receptor expression ↑ 1α- and β-ATPase expression ↓ renal and adrenal 11-βHSD2 expression	108,174–176
Uterine artery ligation/embolization	↑ proapoptotic gene expression ↓ antiapoptotic gene expression Altered gene methylation Altered renin-angiotensin gene expression	177,178
Maternal diabetes/hyperglycemia	↓ IGF-11/mannose-6-phosphate receptor expression Altered IGF-11 activity/bioavailability Activation of NF-κB	64,179,180
Gestational drug exposure		181–184
gentamicin	↓ branching morphogenesis	
β lactams	↑ mesenchymal apoptosis	
cyclosporine	Arrest of nephron formation	
ethanol	? via reduced vitamin A levels	
COX2 inhibitors	Affects prostaglandins	

11-βHSD2, 11β-hydroxysteroid dehydrogenase 2; COX, cyclooxygenase. Adapted from: Luyckx VA, Brenner BM: Nephron endowment. In: *The Kidney*, 8th Ed., edited by Brenner BM, Philadelphia, W.B. Saunders, 2008, pp 654–673.

Table 2. Nephron numbers in humans and associations with BP and birth weight

Age (years)	Ethnicity (Location)	Group	Mean $N_{\text{glom}}$	$\Delta N_{\text{glom}}$	Birth Weight	BP	Reference
0 to 1	White/black (United Kingdom, Cuba, United States)	IUGR versus NBW	635,000 versus 903,000	↓ 13 to 35%	↓	–	44,47,49
16 to 87	White (Denmark)	Normal population	617,000 ± 155,000	–	–	–	37
18 to 89	White, black, Aboriginal (United States, Australia)	White versus black versus Aboriginal	855,183 ± 295,247 versus 921,708 ± 318,089 versus 733,484 ± 217,763	↓ with ↓ birth weight, ↑ age, female, ↓ height	Variable	–	45
34 to 87	White (Denmark)	Type 2 diabetes versus control	673,000 ± 200,000 versus 670,000 ± 176,000	↑ $V_{\text{glom}}$ NS	NBW	–	185
35 to 59	White (Germany)	Hypertensive versus normotensive	746,468 ± 133,240 versus 1,402,360 ± 346,357	↓ 47%	–	↑	41
30 to 65	White (United States)	Hypertensive versus normotensive	747,727 ± 271,155 versus 894,339 ± 275,956	↓ 16%	NBW	↑	43,69
30 to 65	Black (United States)	Hypertensive versus normotensive	912,480 ± 350,329 versus 931,463 ± 290,529	NS	NBW	↑	43,69
30 to 65	White (United States)	White versus black	861,879 ± 306,250 versus 917,789 ± 326,672	NS	NBW	–	43
>18	Australian	Aboriginal versus non-Aboriginal	683,174 ± 130,220 versus 885,318 ± 114,433	↓ 30%	LBW	–	65
>18	Australian Aboriginal	Hypertensive versus normotensive	631,321 ± 105,298 versus 843,324 ± 199,384	↓ 30%	LBW	↑	45
20 to 70	African (Senegal)	Normal population	925,483 ± 225,427	–	–	–	75

$\Delta N_{\text{glom}}$  change in nephron number between groups.

36th weeks.<sup>46</sup>  $N_{\text{glom}}$  at birth is therefore influenced by the intrauterine environment and gestational age. It is generally thought in humans, unlike rodents, that no new nephrons are formed after birth. This question was addressed in a cohort of 56 extremely preterm infants compared with 10 term infants.<sup>47</sup> Radial glomerular counts are lowest in preterm compared with term infants and correlate with gestational age. Furthermore, evidence of active glomerulogenesis is present only up to day 40 of life, suggesting that nephrogenesis ceases at this stage.<sup>47</sup> Further analysis, stratified by presence or absence of renal failure in infants who survived beyond 40 days, found significantly fewer, larger glomeruli in kidneys with renal failure, suggesting either that renal dysfunction impairs glomerulogenesis or that fewer glomeruli may have lowered the threshold for renal failure in extremely ill infants.<sup>47</sup> In contrast, other authors did not find any increase in nephrogenesis between kidneys at birth or 1 year of age, suggesting that renal arrest occurs after birth.<sup>48,49</sup> At both time points, however, growth-restricted infants had significantly fewer nephrons than control infants. A third study again confirmed a significant direct correlation between  $N_{\text{glom}}$  and birth weight and a strong inverse correlation between glomerular volume ( $V_{\text{glom}}$ ) and  $N_{\text{glom}}$  in both black and white neonates.<sup>44</sup> Taken together, these studies of infant kidneys support the hypothesis that an adverse intrauterine environment, manifest as LBW or preterm birth, associates with a congenital reduction in  $N_{\text{glom}}$ , which persists postnatally.

Among 140 adults who were aged 18 to 65 years, a significant positive correlation was found between birth weight and  $N_{\text{glom}}$  with consistent inverse correlation between  $N_{\text{glom}}$  and glomerular size.<sup>43</sup> When stratified by race, mean  $N_{\text{glom}}$  did not differ between black and white individuals, although the distribution among black individuals seemed bimodal, whereby some outliers had very high  $N_{\text{glom}}$  and others had  $N_{\text{glom}} < 500,000$  per kidney. The distribution among white individuals was more normal, and no normal individual had  $< 500,000$

nephrons. Importantly, the relationship between LBW and  $N_{\text{glom}}$  in adults could not be addressed, because all individuals had normal birth weight (NBW).<sup>43</sup> The finding of similar mean  $N_{\text{glom}}$  between white and black individuals has been used to try to discount the hypothesis that low  $N_{\text{glom}}$  contributes to the higher prevalence of hypertension and CKD among black individuals. It is more likely, however, that because LBW is more prevalent among black individuals, this cohort is more representative of the general white population than of the general black population, having included only individuals of NBW.<sup>17</sup>

People who are born with severe nephron deficits, such as unilateral renal agenesis, develop progressive proteinuria, glomerulosclerosis, and renal dysfunction with time.<sup>50,51</sup> Analogously, people who are born with  $N_{\text{glom}}$  at or below the median level may be more susceptible to postnatal factors that act as additional events.<sup>52</sup> Arguing against this, in experimental animals, surgical removal of more than one kidney under varying circumstances and in different species does not always lead to hypertension and renal disease, and, in humans, uninephrectomy is accompanied by hypertrophy and hyperfunction of the remaining kidney, often with little adverse consequences, although hypertension, proteinuria, and renal dysfunction have been reported.<sup>38,53–56</sup> Nonetheless, uninephrectomy *in utero* or early in the postnatal period in animals, in effect, loss of nephrons when nephrogenesis is not yet completed, does lead to adult hypertension and is associated with higher  $V_{\text{glom}}$  and persistence of immature glomeruli into adulthood.<sup>57–60</sup> These data suggest renal compensatory mechanisms for nephron loss may be different while nephrons are developing, as compared with when nephrogenesis is completed, and that extrapolations from the relative safety of adult uninephrectomy may not be applicable in those with congenital nephron deficits.

### Clinical Correlates of Nephron Number

Glomerular counting techniques are performed on autopsy samples, and, to date,

no validated technique allows determination of  $N_{\text{glom}}$  *in vivo*. In animal models, low  $N_{\text{glom}}$  and associations with adverse outcomes have been described in the setting of NBW; therefore, among humans, if birth weight is the only surrogate used, then the impact of  $N_{\text{glom}}$  on any outcome is likely to be underestimated.<sup>61</sup> Current clinical surrogates for  $N_{\text{glom}}$  beyond birth weight are outlined in Table 3.

### Anthropomorphic Factors

LBW and preterm birth associate with reduced  $N_{\text{glom}}$  in various human populations, as outlined already. In addition, HBW may be a risk factor for reduced  $N_{\text{glom}}$ .<sup>62–64</sup> Adult height also associates with birth weight, and  $N_{\text{glom}}$  correlates significantly with adult height among Australian Aboriginals, and male adults have an increase of 28,000 glomeruli per centimeter increase in height.<sup>45,65</sup> Hypertension and diabetic nephropathy are also more prevalent in shorter individuals<sup>66–68</sup>; therefore, these factors should be taken into account when assessing renal risk.

### Glomerular Volume

$V_{\text{glom}}$  consistently varies inversely with  $N_{\text{glom}}$ , suggesting that larger glomeruli reflect compensatory hyperfiltration and hypertrophy that occur when  $N_{\text{glom}}$  are reduced.<sup>40,41,44,46,69</sup> Indeed, total filtration surface area is not different among individuals with varying  $N_{\text{glom}}$ , because kidneys with fewer nephrons have larger glomeruli.<sup>40</sup> Persistent glomerular enlargement, however, can be maladaptive, and large glomeruli are more prevalent

**Table 3.** Clinical surrogates for low nephron number and susceptibility to hypertension and renal disease in humans

Low birth weight <sup>44,47,49</sup>
Preterm birth <sup>47,49</sup>
Short stature <sup>45,67,68</sup>
Low kidney mass <sup>37,78</sup>
Reduced kidney volume <sup>79,80</sup>
Glomerulomegaly <sup>42,44,49</sup>
Gene polymorphisms: <i>PAX2</i> , <i>RET</i> <sup>78,82</sup>
Maternal gestational hyperglycemia, HBW <sup>62,118</sup>

among black donors and predictors of poorer outcomes after transplantation.<sup>70</sup> Consistently, glomerulomegaly is frequent in renal biopsies from Australian Aborigines, in whom LBW and renal disease are highly prevalent, and also associates with a more rapid decline of GFR in Pima Indians.<sup>71–73</sup> Within a kidney, however, individual  $V_{\text{glom}}$  varies considerably, with greater heterogeneity correlating with lower  $N_{\text{glom}}$ , hypertension, body size, and black race.<sup>45</sup> Intraindividual variability among black individuals, however, is high with both low and high nephron number.<sup>69,74,75</sup> Glomerular size may therefore be an independent or additional risk factor predisposing to hypertension and renal disease in populations of African origin, potentially affected by other programmable factors such as modulation of glomerular flow and salt sensitivity.<sup>69,74–77</sup> Evidence of glomerular enlargement in the absence of other potential causes, therefore, should raise the possibility of low  $N_{\text{glom}}$ .

### Renal Mass and Volume

Renal mass and  $N_{\text{glom}}$  correlate significantly in infants who are younger than 3 months, as well as in normal adults.<sup>37,78</sup> Renal mass is therefore proportional to  $N_{\text{glom}}$ , but both are measurable only *ex vivo*. Renal volume is proportional to renal mass; therefore, renal volume has been used as an *in vivo* surrogate for  $N_{\text{glom}}$ .<sup>37</sup> Ultrasound of kidney size and growth postnatally, in preterm children or children who are small for gestational age (SGA) compared with children who are appropriate weight for gestational age (AGA) at 0, 3, and 18 months, found that weight for gestational age correlated with kidney volume at all three time points.<sup>79</sup> Slight catch-up kidney growth is observed in SGA infants but not in preterm infants. Similarly, in Australian Aboriginal children, LBW associates with smaller kidneys on sonograms.<sup>80</sup> Comparison of renal volume between children who were aged 9 to 12 years and born preterm, either SGA or AGA, and control subjects, however, found that kidneys were smallest in those who had been preterm and SGA, but significance

was lost when adjusted for body surface area (BSA).<sup>81</sup> A small kidney, therefore, may be a surrogate for low  $N_{\text{glom}}$ , but growth in kidney size on ultrasound cannot distinguish between normal growth with age and hypertrophy, potentially confounding this association.

### Genetic Polymorphisms

Common polymorphisms of the *PAX2* and *RET* genes, both involved in branching of the ureteric bud, are associated with a 10% reduction in renal volume and may therefore associate with reduced  $N_{\text{glom}}$ .<sup>78,82</sup>

### NEPHRON NUMBER AND BP

In white adults who died of trauma,  $N_{\text{glom}}$  per kidney was significantly lower and  $V_{\text{glom}}$  significantly higher in 10 individuals with hypertension compared with 10 matched individuals with normotension (Table 2).<sup>41</sup> Although mean  $N_{\text{glom}}$  in control subjects were high and birth weights were unknown, this study strongly supports an association between low  $N_{\text{glom}}$  and hypertension in humans. Similarly, among Australian Aborigines,  $N_{\text{glom}}$  was lower and  $V_{\text{glom}}$  higher among those with hypertension.<sup>65</sup> Among 63 individuals, significant correlations between birth weight and  $N_{\text{glom}}$ , mean arterial pressure, and  $N_{\text{glom}}$  and between mean arterial pressure and birth weight were found among white but not black individuals.<sup>43</sup> Among black individuals who had  $N_{\text{glom}}$  below the mean, however, twice as many had hypertension as normotension, suggesting a likely contribution of lower  $N_{\text{glom}}$  to hypertension in this group.<sup>43</sup> Subsequently, the same authors found an association between birth weight and  $N_{\text{glom}}$  but not between  $N_{\text{glom}}$  and BP among both white and black individuals.<sup>76</sup> Although mean birth weights were similar between races in this study, the range was greater among black individuals, suggesting more LBWs and HBWs. The relationship of BP with  $N_{\text{glom}}$  in black individuals therefore is not as clear as among other populations.

$N_{\text{glom}}$  has not been studied in black individuals with LBW, however, except for a small cohort of neonates in whom  $N_{\text{glom}}$  was lower with LBW.<sup>44</sup> With more data, a similar relationship may emerge in adults; however, other factors likely contribute to the increased severity of hypertension in black populations. Conversely, a higher  $N_{\text{glom}}$  seems to be protective against hypertension in white and Aboriginal Australians, making  $N_{\text{glom}}$  a likely crucial factor in pathogenesis of hypertension in these populations.<sup>45</sup>

### BIRTH WEIGHT AND BP

Epidemiologic evidence now strongly supports a relationship between LBW and higher BPs in populations of varied ethnic and geographic origins.<sup>34,83–87</sup> The majority of studies have been conducted of white populations, although studies of various black populations support the inverse relationship between birth weight and BP.<sup>88–91</sup> A similar association has been reported for black children in some studies, but not all, suggesting additional factors affect BP in this population.<sup>92–96</sup> Consistently, however, BPs are highest in those who were of LBW and exhibited fastest postnatal weight gain, demonstrating the importance of early postnatal nutrition in developmental programming.<sup>97–99</sup>

Differences in BP between people of LBW and NBW are amplified with age, with the result that LBW adults often develop overt hypertension.<sup>100</sup> The nephron number hypothesis suggests that reduced renal sodium excretory capacity is a link between  $N_{\text{glom}}$  and hypertension. In animal studies, salt sensitivity has been demonstrated in some programming models but not others but seems to increase with age.<sup>101–104</sup> In humans, emerging evidence supports an association between salt sensitivity and LBW.<sup>105,106</sup> From animal data, this relationship not only may depend on filtration surface area but also is likely affected by altered expression of renal sodium transporters or modulation of the renin-angiotensin-aldosterone system (Table 4).<sup>85,107–112</sup>

**Table 4.** Proposed mechanisms for developmental programming of BP

Programmed Characteristic	Proposed Mechanism/Evidence Affecting BP in Programmed Offspring versus Control Subjects	Reference
Reduced nephron number	Reduced filtration surface area Renal dysfunction	10,18,41,43
Increased renal vascular reactivity	↑ renal artery response to $\beta$ -adrenergic stimuli and sensitivity to adenylyl cyclase in growth-restricted rats	184,186,187
Altered vascular reactivity	↓ flow-mediated dilation in LBW children ↑ uric acid Endothelial dysfunction	107,188–190
Altered RAS	Impaired vascular structure and capillary density Administration of inhibitors of RAS abrogates later hypertension Administration of angiotensin II causes increased hypertensive response Evidence of expression of AT1R and AT2R and ACE activity are divergent at different stages and in different models of programming Overall, programmed suppression of intrarenal RAS during nephrogenesis and postnatal upregulation of AT1R are most consistent	4,30,111,177,191
Altered sodium handling	↓ fractional excretion of sodium ↑ expression of BSC1 and TSC ↑ expression of glucocorticoid receptor ↑ expression of glucocorticoid responsive $\alpha$ 1 and $\beta$ 1 subunits of Na/K-ATPase ↑ expression of NHE3 ↑ expression of $\beta$ and $\gamma$ ENaC	22,109,110,174,192
Increased sympathetic nervous system activity	Renal denervation reduced systolic BP and sodium transporter expression	193
Catch-up growth/obesity	Higher BP in children who catch up fastest Reduced flow-mediated dilation with higher rate of weight gain	98,154

AT1R, angiotensin subtype 1 receptor; AT2R, angiotensin subtype 2 receptor; BSC1, bumetanide-sensitive co-transporter; ENaC, epithelial sodium channel; NHE3, sodium hydrogen exchanger; RAS, renin-angiotensin system; TSC, thiazide-sensitive co-transporter.

## BIRTH WEIGHT AND RENAL OUTCOMES

Birth weight influences a variety of renal parameters, particularly proteinuria, renal function, and kidney disease.

### Proteinuria

Multiple studies showed an increased prevalence of microalbuminuria and proteinuria among LBW adults.<sup>15,71,113–117</sup> The earliest evidence from Australian Aboriginals found an odds ratio of 2.8 for macroalbuminuria in those who had been of LBW compared with NBW.<sup>15,71,113,114</sup> In addition, the degree of albuminuria predicted loss of renal function and strongly correlated with mortality.<sup>71,72</sup> Similarly, among Pima Indians with type 2 diabetes, the prevalence

of albuminuria was higher in those who had birth weights <2500 or >4500 g compared with those of NBW.<sup>115</sup> Gestational exposure to maternal diabetes was the strongest risk factor for proteinuria among those with HBW and has been confirmed in other studies.<sup>118</sup> Gestational diabetes in animal models was associated with a reduced  $N_{\text{glom}}$  in offspring.<sup>62</sup> This programming mechanism is not yet proved in humans.

### Measures of Renal Function

Clearance of amikacin, used as a surrogate for GFR in 1-day-old neonates, correlates significantly with birth weight and gestational age, suggesting impairment of GFR with preterm birth or IUGR.<sup>119</sup> In longer term follow-up of children with very low birth weight

(VLBW; <1000 g), serum creatinine was higher and GFR lower compared with age-matched NBW children at 6 to 12 years.<sup>120</sup> A stronger association was found using cystatin C in children, suggesting that creatinine-based formulas underestimate the impact of birth weight on GFR.<sup>121,122</sup> In young female adults who were preterm, SGA, or normal term infants, GFR tended to be lower in the SGA group and albuminuria higher in the preterm and SGA groups, although not statistically significant.<sup>123</sup> In a larger study of 19-year-olds who were very preterm, stratified by weight for gestational age, birth weight correlated negatively with serum creatinine and albuminuria and positively with GFR.<sup>124</sup> These results are consistent with those of others, but as has been shown in animal studies, pro-

gramming effects seem greater in males.<sup>125</sup> Renal functional reserve was measured in 20-year-olds who had been preterm and either SGA or AGA or had been term and NBW by measuring GFR and effective renal plasma flow before and after dopamine infusion or an amino acid load.<sup>126</sup> The relative increase in GFR tended to be lower in SGA compared with AGA and control subjects, and effective renal plasma flow was lower in both groups of preterm subjects, although not statistically significant in this small study. These results are potentially consistent with reduced renal reserve capacity in kidneys of LBW and preterm individuals, possibly a result of reduced  $N_{glom}$ .

For dissection of the relative contribution of environment *versus* genetics on programming, renal function was evaluated in 265 twin pairs at 26 years of age.<sup>127</sup> GFR measured by creatinine clearance was significantly lower in LBW compared with NBW twins. Furthermore, birth weight differences correlated positively with GFR within both monozygotic and dizygotic pairs, suggesting that fetoplacental factors have an independent impact on renal function.<sup>127</sup>

The importance of early extrauterine nutrition is highlighted in a cohort of preterm infants who were born either with VLBW or before 30 weeks of gestation, stratified by IUGR, extrauterine growth restriction, or AGA with normal growth.<sup>128</sup> At 7.6 years, renal volume and iothalamate GFR were significantly lower among both groups of perinatally growth-restricted children, emphasizing that the window for renal programming extends into the early perinatal period in preterm neonates and highlights the critical impact of early nutrition.<sup>128</sup>

### Chronic Kidney Disease

LBW is associated in animals with accelerated progression of Thy-1 nephritis and greater maladaptive responses to induced hyperglycemia and diabetes, consistent with a greater susceptibility to renal injury in the setting of reduced  $N_{glom}$ .<sup>63,129,130</sup> Interestingly, in old LBW diabetic rats, podocyte density was re-

duced and the average area covered by each podocyte was greater compared with NBW diabetic controls.<sup>130</sup> A similar finding of “podocyte insufficiency” was a contributor to rapid progression of diabetic nephropathy among Pima Indians.<sup>73</sup> This finding was not correlated with  $N_{glom}$  in humans but may be a consequence of programmed renal changes in this population. Increased susceptibility to hyperfiltration and glomerulosclerosis associates with preterm birth and LBW in a series of six patients with secondary FSGS and glomerulomegaly, a likely consequence of programmed nephron deficits.<sup>131</sup> Several studies described an increased susceptibility to diabetic nephropathy among individuals of LBW or those with short stature.<sup>67,115,132</sup> More rapid progression or relative resistance to therapy was also observed in LBW individuals with IgA nephropathy, membranous nephropathy, minimal-change disease, nephrotic syndrome, and chronic pyelonephritis.<sup>132–138</sup> Among a predominantly black dialysis population, the odds ratio for ESRD was 1.4 (95% confidence interval 1.1 to 1.8) among those with LBW compared with those with NBW.<sup>16</sup> This relationship persisted for all causes of ESRD and was not affected by family history of ESRD. The odds ratio for diabetic renal disease was 2.4 for those who had birth weights  $\geq 4000$  g.<sup>16,139</sup> A retrospective analysis of  $>2$  million Norwegian children reported a relative risk for ESRD of 1.7 in those with birth weights  $<10$ th percentile.<sup>9</sup> A birth weight of  $\geq 4.5$  kg associated with an increased risk for ESRD only in female individuals. A recent meta-analysis of 31 studies found that individuals with LBW had a 70% increased risk for developing CKD, defined as albuminuria, reduced GFR, or ESRD.<sup>10</sup> In most studies, the birth weight effect was greater in male individuals.<sup>8–10</sup> Mechanisms for the programmed gender differences are reviewed elsewhere.<sup>140</sup> These large cohorts also underscore the U-shaped relationship between risk for CKD and birth weight, indicating increased risk with both LBW and HBW.<sup>8,16,115</sup>

### NEPHRON ENDOWMENT IN RENAL TRANSPLANTATION

Prescription of kidneys on the basis of the physiologic capacity of the donor organ to meet the metabolic needs of a recipient is not generally considered, despite evidence in animals that nephron mass of the transplanted kidney has an independent impact on outcome.<sup>141–144</sup> To investigate this possibility, several investigators compared recipient and donor BSA, kidney weight, or renal volume as surrogates for metabolic demand and nephron mass. Allograft failure was greater when kidneys were transplanted from small donors into large recipients compared with size-matched donor–recipient pairs.<sup>145</sup> BSA, however, was not always proportional to kidney weight; therefore, ratios of donor-to-recipient BSA may not truly reflect supply and demand. Kidney weight is an acceptable surrogate for nephron mass.<sup>37</sup> Analysis of the ratio of donor kidney weight to recipient body weight (DKW/RBW) in living-donor transplants revealed that a DKW/RBW  $>4.5$  g/kg is significantly associated with better outcomes at 3 years compared with a ratio  $<3.0$  g/kg.<sup>146</sup> Similarly, among recipients of cadaveric kidneys, proteinuria was significantly higher and developed earlier in those with DKW/RBW  $<2$  g/kg as compared with those with higher ratios, although 5-year graft survival was not different.<sup>147</sup> An ultrasound-based calculation of nephron dose index (Tx/W) incorporating cadaveric transplant kidney cross-sectional area (Tx) and recipient body weight (W) highlighted significantly better allograft function at 5 years in those with higher compared with lower Tx/W.<sup>148</sup> These data suggest small kidneys transplanted into large recipients may not have an adequate capacity to meet the metabolic needs of the recipient without imposing glomerular hyperfiltration, which may eventually contribute to nephron loss and allograft failure.<sup>84,149</sup> Transplanted nephron mass not only may be a function of congenital endowment of the donor, but also may be affected by loss of nephrons with age and renal injury. All of these factors should be closely consid-

ered, in addition to immunologic matching, in selection of appropriate recipients in whom the allograft is likely to function for the longest time.

Living-donor kidney selection does not affect only the recipient. Although donation is generally safe, small increases in BP and proteinuria do occur.<sup>55</sup> The safety of kidney donation in the setting of low  $N_{\text{glom}}$  has not been studied rigorously. Retrospective analysis of donor outcomes from the Northern Territory of Australia found that long-term outcomes are significantly worse, including ESRD and death, among indigenous compared with nonindigenous donors.<sup>56</sup> All donors had normal renal function at screening; therefore, loss of one kidney may be associated with significant morbidity in the indigenous population.  $N_{\text{glom}}$  is lower in the Aboriginal Australian population and strongly associates with LBW.<sup>65,71,72</sup> This important article should raise significant concerns as to the safety of living kidney donor programs in populations with high prevalence of LBW and kidney disease.<sup>56</sup>

## INTERGENERATIONAL PROGRAMMING

Offspring of LBW mothers are more likely to be born with LBW.<sup>150</sup> In addition, mothers who have poor perinatal outcomes, especially VLBW infants or preeclampsia, have a higher risk for requiring a kidney biopsy or developing ESRD in the future.<sup>151,152</sup> The risk for preeclampsia, preterm birth, or IUGR increases in mothers with renal dysfunction and hypertension.<sup>153</sup> It is plausible, therefore, that, in turn, these infants will be at increased risk for hypertension and kidney disease, perpetuating a vicious circle.

## IMPACT OF CATCH-UP GROWTH

Many studies support the finding that rapid increases in weight after birth associates with an increased risk for subsequent high BP and cardiovascular disease.<sup>98,99,154–156</sup> Evidence from rodents demonstrated an accelerated senescence

in kidneys, hearts, and aortas and premature mortality in LBW offspring experiencing rapid catch-up growth.<sup>157–160</sup> This has not been rigorously studied in humans. Leukocyte telomere lengths are not different between SGA and AGA infants at birth, but telomeres are shorter in SGA children at 5 years, suggesting programmed accelerated senescence, likely as a consequence of catch-up growth and increased oxidative stress, may also contribute to developmental programming of adult disease.<sup>161–164</sup>

## CONCLUSIONS

The association between an adverse fetal and early postnatal environment and hypertension and renal disease in later life is now quite compelling and seems to be mediated, at least in part, by impaired nephrogenesis. Whether the increased risk for CKD is a direct consequence of altered renal development or a cumulative process resulting from other effects of programming such as diabetes and hypertension followed by later hits, superimposed on reduced  $N_{\text{glom}}$  and glomerular hypertrophy, is not yet clear. Other factors, such as increased oxidative stress, renal inflammation, accelerated senescence, and catch-up growth, all likely contribute to eventual renal disease.<sup>165–167</sup>

$N_{\text{glom}}$  in humans varies widely, suggesting that a significant proportion of the general population, especially in areas where HBWs or LBWs are prevalent, may be at risk for developing hypertension and renal disease. Measurement of  $N_{\text{glom}}$  *in vivo* remains difficult. The best surrogate markers for low  $N_{\text{glom}}$  thus far are LBW; short stature; reduced kidney volume on ultrasound, especially in children; and glomerulomegaly on kidney biopsy. A kidney with a reduced complement of nephrons would also have less renal reserve to adapt to dietary excesses or to compensate for renal injury.

Although  $N_{\text{glom}}$  is a nonmodifiable factor to the clinician, increased awareness may lead to changes in practice that could have far-reaching consequences.<sup>168</sup> Neonates in intensive care units are

often small and preterm and receive nephrotoxic medications (nonsteroidal anti-inflammatory drugs, aminoglycosides) that may affect nephrogenesis. It may be time to develop safer treatment protocols especially for infections. Early postnatal nutrition should be modified to optimize growth and avoid extrauterine growth restriction. Rapid catch-up growth and obesity should be avoided in children who are born small through parental education and support. Appropriate lifestyle lessons learned as children will be beneficial as these individuals age. Long-term outcomes of donors and recipients of renal allografts should be maximized by considering nephron endowment and matching to recipient demand. That even seemingly minor influences during development can have major consequences on nephrogenesis underscores the critical importance of optimization of perinatal care and early nutrition, which have a major impact on population health in the future.

## DISCLOSURES

None.

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See related editorial, "Size Matters in Renal Allograft Survival," on pages 890–891, and related article, "Kidney and Recipient Weight Incompatibility Reduces Long-Term Graft Survival," on pages 1022–1029.