CLINICAL IMPLICATIONS OF BASIC RESEARCH

Low Nephron Number and Its Clinical Consequences

**Valerie A. Luyckx, M.B.B.Ch.[1]*, Khuloud Shukha, M.D.[2],
and Barry M. Brenner, M.D.[3]**

[1]**Associate Professor, Division of Nephrology, University of Alberta, Edmonton, Alberta, Canada;
[2]Internal Medicine Resident, Mount Auburn Hospital, Cambridge, MA, USA; and [3]Samuel A. Levine
Distinguished Professor of Medicine Renal Division, Brigham and Women's Hospital, Harvard
Medical School, Boston, MA, USA*

ABSTRACT

Epidemiologic studies now strongly support the hypothesis, proposed over two decades ago, that
developmental programming of the kidney impacts an individual's risk for hypertension and renal
disease in later life. Low birth weight is the strongest current clinical surrogate marker for an adverse
intrauterine environment and, based on animal and human studies, is associated with a low nephron
number. Other clinical correlates of low nephron number include female gender, short adult stature,
small kidney size, and prematurity. Low nephron number in Caucasian and Australian Aboriginal sub-
jects has been shown to be associated with higher blood pressures, and, conversely, hypertension is less
prevalent in individuals with higher nephron numbers. In addition to nephron number, other pro-
grammed factors associated with the increased risk of hypertension include salt sensitivity, altered
expression of renal sodium transporters, altered vascular reactivity, and sympathetic nervous system
overactivity. Glomerular volume is universally found to vary inversely with nephron number, suggesting
a degree of compensatory hypertrophy and hyperfunction in the setting of a low nephron number. This
adaptation may become overwhelmed in the setting of superimposed renal insults, e.g. diabetes mellitus
or rapid catch-up growth, leading to the vicious cycle of on-going hyperfiltration, proteinuria, nephron
loss and progressive renal functional decline. Many millions of babies are born with low birth weight

Conflict of interest: No potential conflict of interest relevant to this article was reported.
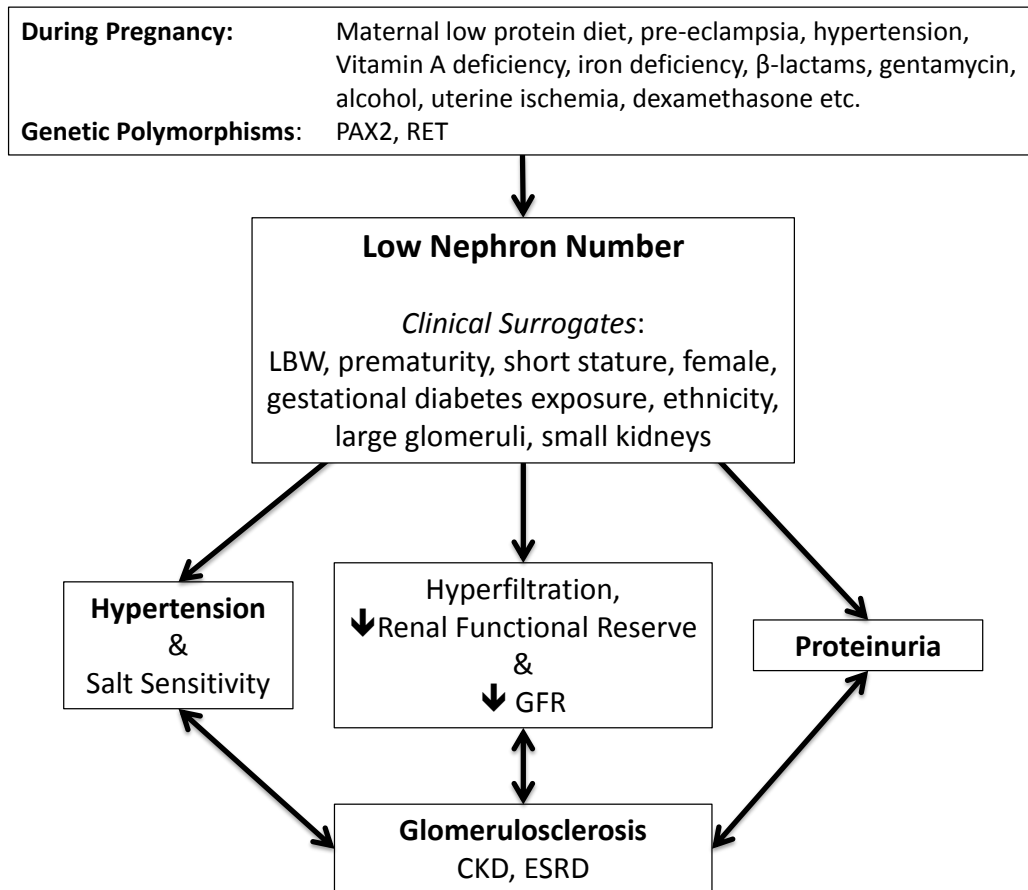
* To whom correspondence should be addressed. **E-mail:** vluyckx@ualberta.ca

every year, and hypertension and renal disease prevalences are increasing around the globe. At present, little can be done clinically to augment nephron number; therefore adequate prenatal care and careful postnatal nutrition are crucial to optimize an individual's nephron number during development and potentially to stem the tide of the growing cardiovascular and renal disease epidemics worldwide.

KEY WORDS: Low birth weight, nephron number, developmental programming, hypertension, renal disease, kidney size

In 1988, Brenner, Anderson, and Garcia suggested that a low nephron number, acquired *in utero*, may be a common denominator in populations with high susceptibility to hypertension and renal disease.[1] Such a kidney with fewer nephrons, and hence a low filtration surface area, would have a reduced capacity to excrete sodium, inducing a hypervolemic state, thereby contributing to the development of hypertension (Figure 1). Animal experiments and epidemiological data have accumulated in support of this "nephron number" hypothesis.[2–8] Nephron number varies surprisingly widely among individuals, more, for example, than height or weight, with a variability of up to 10-fold within select populations.[5,6,9–17] An individual's nephron number is the result of a complex interplay between genetics and environment that plays out through their lifetime, carrying the

During Pregnancy:	Maternal low protein diet, pre-eclampsia, hypertension, Vitamin A deficiency, iron deficiency, β-lactams, gentamycin, alcohol, uterine ischemia, dexamethasone etc.
Genetic Polymorphisms:	PAX2, RET

Low Nephron Number

Clinical Surrogates:
LBW, prematurity, short stature, female, gestational diabetes exposure, ethnicity, large glomeruli, small kidneys

Hypertension & Salt Sensitivity

Hyperfiltration, ↓Renal Functional Reserve & ↓ GFR

Proteinuria

Glomerulosclerosis
CKD, ESRD

Figure 1. Known causes of low nephron number.

Schematic diagram outlining the known causes of low nephron number, derived from human and animal studies, current clinical surrogate markers for low nephron number, and clinical consequences of low nephron number, reduced filtration surface area, and abnormal glomerular development.

imprint of their past, being reflected in their present renal function, and impacting their future risk of hypertension and kidney disease.

DETERMINANTS OF NEPHRON NUMBER

Prenatal Life and Birth Weight

Kidney development in humans begins in the 9th week and ends around the 36th week of gestation.[5] There is no evidence for postnatal nephrogenesis in humans, except in extremely preterm infants in whom abnormal nephrogenesis was observed until day 40 after birth.[16,18] Similarly, in preterm baboons followed for 21 days after birth, nephrogenesis did continue, but the proportion of immature, poorly vascularized and abnormal glomeruli was increased compared to gestational controls.[19] In young adult rats exposed to a low protein diet *in utero*, glomerulogenesis was retarded with a higher proportion of immature nephrons, associated with abnormalities in the glomerular basement membrane and podocyte structure.[20] These authors postulate that such subtle structural abnormalities programmed early on may increase susceptibility to on-going renal injury.

Numerous studies have investigated events and changes during pregnancy that lead to reduced nephron number, including maternal diets deficient in protein, iron, or vitamin A, uterine artery ligation, maternal hyperglycemia, prenatal exposure to glucocorticoids and drugs such as gentamycin, cyclosporin, β-lactams, ethanol, and cox2 inhibitors.[21–36] Many of these interventions also result in low birth weight (LBW) offspring.

The World Health Organization defines LBW as a birth weight under 2,500 g; thus an infant can have a LBW by being born premature (before the 37th week of gestation), although at an appropriate weight for gestational age (AGA), or due to intrauterine growth restriction (IUGR) during a term pregnancy.[37] A small for gestational age infant (SGA) is defined as weighing less than the 10th percentile of the normal weight for gestation.[37] Risk factors for LBW are many: in the Third World mostly related to maternal malnutrition, inadequate prenatal care, infections, etc., and in the First World also related to higher-risk pregnancies, prematurity, and advanced maternal age.[37–40] Interestingly, maternal LBW in both whites and blacks in the US was a risk factor for infant LBW, prematurity, and IUGR, regardless of economic environment, demonstrating the impact of developmental programming across generations.[41]

In humans, nephron numbers were found to be lower in neonates with LBW.[12,16,42] Gestational age also correlates with nephron number, and prematurity results in reduced nephron endowment.[16] In adults, nephron number has not been reported in those of LBW, but several studies have shown a strong direct correlation with birth weight across the normal birth weight range among Australian Aborigines, Caucasians, and people of African origin.[11,12,16,43] One large study calculated an increase of 257,426 glomeruli per kilogram increase in birth weight.[11] More human studies are required including diverse populations and a broad spectrum of birth weights to define further this relationship.

At the other extreme, high birth weight (HBW), defined as a birth weight > 4,000 g, has also been associated with adverse long-term renal outcomes, although the relationship with nephron number in humans is not known.[44,45] HBW is often the result of maternal hyperglycemia, and, in animals, offspring of diabetic dams have been found to have reduced nephron numbers.[46–48]

Genetics

Important pathways in nephrogenesis include GDNF/RET, FGF, PAX2, HH, and others which have been expertly reviewed elsewhere.[49] Polymorphisms in several of these genes have been investigated in relation to kidney size and nephron number in humans. PAX2 has a wide range of functions in kidney development, and a common variant in the population, the AAA haplotype, reduces PAX2 mRNA expression and causes a 10% reduction in kidney volume.[50,51] Similarly, RET is essential for branching nephrogenesis, and a polymorphic variant, *RET*[1476A], is associated with an almost 10% reduction in kidney volume at birth.[52] Kidney volume was found to be proportional to nephron number in this study. Mutations in other genes such as Imx-1, Eya-1, Six1, Sall1, and tcf2 also result in a reduced nephron number, small kidney size, and disorganized renal tissue, in addition to other extrarenal manifestations.[53]

OTHER CLINICAL CORRELATES OF NEPHRON NUMBER

Except for rough estimates of the nephron number by renal MRI or kidney biopsy, an accurate count can only be done post mortem.[15,43,54] In humans, thus far, LBW and prematurity are the strongest clinical correlates of low nephron number. In animals, however, low nephron number has been reported in the absence of LBW, and, conversely, not all LBW animals have reduced nephron numbers; therefore birth weight alone may not be a universal surrogate marker for nephron number.[55,56] Several additional clinical surrogates for nephron number have been examined (Figure 1), which, although not absolute, may also serve to increase awareness of the possibility of low nephron number, with the attendant risks for hypertension and renal disease, and may therefore impact on optimization of other risk factors.

Anthropomorphic Factors

Females are estimated to have 12% fewer glomeruli than males.[43,57,58] Increasing age is associated with a predicted reduction of 3,676 glomeruli per kidney per year after age 18.[15,43] Adult height has been found to correlate positively with nephron number, with an estimated increase of 28,000 glomeruli per centimeter increase in height, and height was found to contribute to two-thirds of the variance in glomerular number.[15,43,58] Birth weight tends to be associated with subsequent height and therefore may be a confounder in this relationship, but adult height is much more readily available than birth weight in clinical practice and therefore useful.[59]

Glomerular Volume

Although nephron number does not increase after birth, the kidney matches its filtration capacity to the body's demands by increasing the glomerular size through hypertrophy.[5,11,12,57,58] As such, mean glomerular volumes have consistently been found to correlate *inversely* with glomerular number and *directly* with current body size.[43] Keller et al. reported a 133% higher mean glomerular volume and a 46.6% reduction in glomerular number in hypertensive subjects, compared to controls.[6] Lower nephron number, black race, hypertension, and body size all correlate with an increase in individual glomerular volume within a single kidney.[14,17,43] Larger glomeruli therefore suggest a lower nephron number, although in African-Americans glomerular volume appears to be globally increased but still in inverse proportion to nephron number, suggesting additional factors contribute to glomerular size in this population.[9]

Kidney Mass

Kidney weight can only be measured *ex vivo*, but from autopsy studies, nephron number correlates directly with kidney weight in adults and children.[15,52] Zhang et al. predicted an increase of 23,459 glomeruli per gram of kidney mass (95% confidence interval 4,590–42,238) in infants 3 months and younger.[52] In living subjects, kidney mass is obtainable by weighing the donor kidney prior to transplantation and has proven to have clinical relevance (*vide infra*).

Kidney Volume

Kidney volume can be readily measured by ultrasound. Spencer et al. found relatively lower kidney volumes in LBW Australian Aboriginal children aged 5–18 when adjusted for body size.[60] In contrast, Rakow et al. did not find a significant difference between kidney volumes of individuals who had been term AGA, term SGA, or preterm, when adjusting for body surface area (BSA), gender, and age.[61] Kidney size is dependent on nephron number and the degree of nephron hypertrophy and is strongly correlated with current body size.[15] In fetuses and at birth, kidney volume is proportional to nephron number; however, subsequently, normal kidney growth (impacted by BSA, age, and gender), glomerulo-megaly (hypertrophy due to low nephron number, obesity, etc.), and nephron loss through injury are likely to affect kidney volume disproportionately, making a direct relationship less clear.[60] Among young adults born prematurely (either AGA or SGA) compared with term age-matched controls, prematurity was associated with smaller kidneys at age 20 years, whereas IUGR had only a small, non-significant effect.[62] Kidney volume may therefore not be ideally reliable as a surrogate for nephron endowment.

CLINICAL CONSEQUENCES OF IMPAIRED DEVELOPMENTAL PROGRAMMING IN THE KIDNEY

Nephron Number, Size, and Blood Pressure

In adult animals, surgical removal of one kidney under varying circumstances and in different species does not always result in spontaneous hypertension and renal disease.[63] In contrast, however, uni-nephrectomy on postnatal day 1 in rats, or fetal uni-nephrectomy in sheep, i.e. loss of nephrons at a time when nephrogenesis is still ongoing, does lead to adult hypertension prior to any evidence of renal injury.[64–66] These data support the possibility that intrauterine or congenital reduction in nephron number may elicit different compensatory responses compared to later nephron loss, augmenting the risk of hypertension. Consistent with this view, kidneys from rats that underwent uni-nephrectomy at day 3 of age had similar total number but a greater proportion of immature glomeruli in adulthood, compared with those who underwent nephrectomy at day 120 of age.[67] In addition, mean glomerular volume in neonatally nephrectomized rats was increased by 59% compared with 20% in adult nephrectomized rats, suggesting a greater degree of compensatory hypertrophy and hyperfunction in response to neonatal nephrectomy. One could argue that as the demand for filtration capacity highly depends on BSA and basal metabolic rate, the increment in BSA from infancy through childhood and adulthood may impose a much greater strain on a smaller kidney early in life, which may demand different and more robust adaptation than during adulthood, when no growth occurs except for changes in weight.[15]

Some suggest that when kidney growth is interrupted, fewer, yet normal, nephrons develop. Others challenge this, as nephrogenesis is a highly complex and regulated process, and expect some structural and/or functional defects in addition to the reduced nephron number. This question is difficult to address, but in GDNF (glial cell-derived neurotrophic factor) heterozygous mice, a model with low nephron number and in which 20% of animals have unilateral renal agenesis, single kidney nephron numbers were found to be identical in mice born with one or two kidneys.[68] Although glomerular filtration rates (GFR) were

similar, salt and water handling were different, suggesting possible alterations in nephron function in the mice with unilateral renal agenesis. In this model, a reduction in nephron number per se was not associated with elevated blood pressures, but when maintained on a high-salt diet GDNF-deficient mice became significantly hypertensive, and blood pressures were highest in those with fewest nephrons.[68] This observation could be interpreted to suggest that a deficit in nephron number may in itself not be enough to result in disease but likely enhances susceptibility to a second "hit", transforming subclinical into overt renal dysfunction.[69]

The association between low nephron number and higher blood pressures has been demonstrated in white adults and in Australian Aborigines but has not been proven among individuals of African origin.[6,43,58,70] To our knowledge, the relationship has not been studied in other ethnic groups. Conversely, a higher nephron number appears to be protective in the Caucasian and Australian Aboriginal populations.[17,43] Similarly, in some animal models restoration of nephron number has been found to abrogate the development of hypertension, suggesting that nephron number is an important factor in the pathogenesis of hypertension.[71–73]

Birth Weight Predicts Later Life Hypertension

Since the 1980s, when the inverse correlation between LBW and hypertension was reported, numerous studies in humans and animals have supported this observation.[2,36,74–79] It is important to note that in LBW children, blood pressures tend to be higher than those of normal birth weight children but are not in the hypertensive range, but with time blood pressures increase and LBW individuals become overtly hypertensive with age. Although preterm birth itself is associated with increased blood pressure, LBW for gestational age has been more strongly associated with higher blood pressures at birth and at 18 months of age than LBW of prematurity, suggesting that an adverse intrauterine environment is an important factor.[80–82] Consistent with this, a recent Swedish study of 16,265 twins found a correlation between LBW and later life hypertension within dizygotic and monozygotic twin pairs, suggesting that individual fetal growth is an important factor,

independent of genetic background, impacting developmental programming of adult disease.[83] Not all studies confirm the association between birth weight and subsequent blood pressures, however.[84–86] The relationship appears to be least consistent among US black children but is maintained in African and Caribbean black children, suggesting that genetic and/or environmental factors may be more pivotal in the US population.[75,77,78,87]

Importantly, reduced nephron number is not the only link between LBW and hypertension.[3,88] Salt sensitivity has also been shown to be associated with LBW in humans and in some animal models.[68,89,90] Altered expression of renal sodium transporters and modulation of the renin–angiotensin–aldosterone system have been shown in prenatally programmed animals, which may contribute to salt sensitivity.[91–95] Consistent with this, in elegant studies Dagan et al. have shown increased tubule sodium transport to be a likely contributor to high blood pressure in adult animals that were exposed to maternal low-protein diet or prenatal dexamethasone.[96,97] Additional proposed mechanisms for developmental programming of blood pressure, studied mostly in animals but also in humans, include increased renal vascular reactivity, altered vascular reactivity, and increased sympathetic nervous system activity.[33,98–102]

Birth Weight and Renal Outcomes

Proteinuria
Studies in various populations have shown increased urine protein excretion in subjects who had been of LBW, although the significance does not always persist when adjusted for additional risk factors, e.g. current HbA1c in diabetic youth.[80,103] Among Australian Aborigines, albuminuria was found to correlate strongly with LBW and to increase dramatically with age.[104,105] In this population, overt proteinuria was a significant predictor of loss of GFR, renal failure, and natural death.[106,107] Among Pima Indians, a U-shaped association was found between birth weight and albumin excretion in diabetics, i.e. both LBW and HBW (largely due to gestational diabetes) correlated with increased albumin excretion.[44] Podocyte abnormalities have been described in LBW animals, which may play a role in the

development of proteinuria.[20,108] It is likely therefore that intrauterine programming of nephron development may be associated with increased risk of albuminuria.

Measures of Renal Function
A reduction in nephron number, in the absence of compensatory hyperfunction, would be expected to result in a lower total GFR and creatinine clearance, and, indeed, in 1-day-old neonates born premature or SGA, GFRs were found to be impaired compared to normal birth weight neonates.[109] Lower GFR and higher serum creatinine were also found in LBW children, aged 6–12 years, compared with age-matched normal birth weight children.[110] In contrast, however, no significant difference in GFR was found among three groups of 9–12-year-olds who had been either preterm, term SGA, or term AGA.[61] Interestingly, in children, GFR measured by cystatin C was found to correlate better with birth weight than creatinine-based formulas, suggesting the validity of these formulas may need to be re-evaluated in LBW individuals.[111,112] A positive correlation was found, however, between birth weight and creatinine-based GFR in a cohort of young adults, born very premature.[80] Using 24-hour urine creatinine clearance within adult twin pairs, GFRs were found to be lower in the LBW twin, again suggesting an independent effect of the intrauterine environment on programming of renal function.[113]

A small cross-sectional study compared total GFR, effective renal plasma flow, and filtration fraction before and after renal stimulation with low-dose dopamine infusion and oral amino acid intake in 20-year-olds born premature and AGA, premature and SGA, or term and AGA.[114] It would be expected that a kidney with fewer nephrons is already hyperfiltering to some degree, which may abrogate any change in serum creatinine, but would have a blunted increase in GFR when stimulated further. This study was limited by small sample size, but 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 SGA and AGA preterm individuals, although not statistically significant.[115] A recent study of non-diabetic young adults found a significant reduction in renal functional reserve in those with diabetic mothers (i.e. exposed to diabetic milieu *in utero*), compared to those with

diabetic fathers, thereby excluding a genetic confounder, and strongly suggesting a long-term impact of gestational diabetes exposure.[114] The authors postulate that reduced renal functional reserve may reflect a programmed reduction in nephron number in offspring of diabetic mothers. Evaluation of renal functional reserve may therefore be a more sensitive method to detect subtle changes in renal function due to reduced nephron number.

Chronic Kidney Disease

A recent meta-analysis of 31 studies found a 70% increase in relative risk of chronic kidney disease (CKD) with LBW.[116] A U-shaped curve for risk of CKD and birth weight (< 2.5 kg or ≥ 4.5 kg) among adult men, but not women, was found in a large US cohort.[117] Many animal studies of fetal programming also report increased susceptibility to hypertension and renal dysfunction in males, although the reasons for the gender differences are not entirely clear.[118] A retrospective study of over 2 million Norwegians reported a relative risk of end-stage renal disease (ESRD) of 1.7 in males and females born below the 10th percentile in weight, but only in females with birth weights > 4.5 kg.[119] A U-shaped curve was also described between birth weight and ESRD in both males and females in a predominantly black US population.[120]

Epidemiologic studies therefore support the relationship between high or low birth weights and risk of CKD. A relationship between nephron number and risk of CKD in humans, however, has not been directly studied. Hodgin et al. reported renal biopsy findings in six adults who had been born premature and LBW.[121] They described consistent findings of focal and segmental glomerulosclerosis, associated with glomerulomegaly, most likely on the basis of a congenitally reduced nephron number. Nephron number per se, however, cannot be invoked as the sole cause of renal dysfunction in most patients. A kidney with a reduced nephron complement likely undergoes some degree of hyperfiltration, especially if body size and functional demand are high, and may have subtle structural abnormalities, both of which would enhance susceptibility, or reduce resistance, to additional renal injury or stress (Figure 1). Consistent with this possibility, LBW has been associated with poorer outcomes in patients with nephrotic syndrome, membranous nephropathy, IgA nephropathy, minimal change, and diabetic nephropathy.[45,122–125] Abnormal glomerular adaptation and greater renal injury have also been shown in LBW animals with reduced nephron numbers.[108,126] Suggested cellular and molecular mechanisms for the association between LBW and CKD in adult life include an imbalance between apoptosis and cell proliferation, accelerated senescence, and mitochondrial dysfunction.[127]

Born Small – Stay Small! The Catch-up Effect

The combination of LBW with a rapid increase in weight after birth amplifies the risks for hypertension and cardiovascular disease in later life.[128–130] Rapid weight gain by as early as 2 weeks of age was associated with endothelial dysfunction in the same subjects 16 years later.[131] The "thrifty phenotype hypothesis" states that in the event of a sub-optimal intrauterine environment, embryonic and fetal adaptive responses limit fetal growth, resulting in a phenotype that is better suited to survive under adverse conditions, e.g. nutrient scarcity. These adaptive changes may become maladaptive when the postnatal environment offers better growth conditions, thereby enhancing the risk of hypertension and clinical renal disease.[7,132] Animal models of LBW followed by accelerated postnatal growth have shown enhanced oxidative stress, telomere shortening, and accelerated senescence in kidneys, hearts, and aortas associated with premature death.[133–136] Although more circumstantial, there is evidence pointing to accelerated senescence and increased oxidative stress in LBW humans consistent with "the dangerous road of catch-up growth".[137–140]

Nephron Dosing in Renal Transplantation

In animal models of renal programming, e.g. maternal gestational low-protein diet or uterine artery ligation, offspring nephron numbers are generally reduced by 25%–30%, often resulting in adult hypertension and renal disease, suggesting that loss of a single kidney (i.e. 50% of nephrons) even in a normal individual, may carry similar risk.[2,73] Indeed, long-term follow-up of 52 kidney donors over 10 years did find an increased risk of hypertension and proteinuria.[141] Other reports, predominantly in white kidney donors, have reported a lower risk of hypertension, proteinuria, and renal dysfunction, suggesting that uni-

nephrectomy is safe.[142–145] More recently, however, warning flags have been raised about the possibility of harm of living kidney donation in other ethnic groups. Among Australian Aboriginal kidney donors, after a median of 16 years, the incidence of hypertension, CKD, and ESRD was very high compared to Caucasian donors.[143] Similarly, among Aboriginal Canadian donors, the prevalence of hypertension was significantly more frequent than among Caucasians, with 100% of Aborigines having hypertension 20 years after donation.[146] Estimated GFR was not different between populations in this study, however, although more Aboriginal donors had proteinuria. In US cohorts, hypertension and CKD were significantly more prevalent among black compared to white donors.[147,148] Uni-nephrectomy, therefore, does appear to carry some risk in populations known to be at increased risk of hypertension and kidney disease. These same populations generally have a higher prevalence of extremes of birth weight, low among Australian Aboriginal and US black populations and high in the Canadian Aboriginal population, suggesting that associated low nephron number may be a contributory factor to the increased renal risk post-nephrectomy.

From the recipient's point of view, the importance of nephron mass as an antigen-independent determinant of transplant outcomes, i.e. matching kidney size to the recipient's demand, has not always been accepted.[149] In animal models, independent of immunologic barriers, transplanted nephron mass has a significant impact on allograft survival.[150–152] In humans, various methods have been employed to try to assess the impact of kidney size, utilizing ratios of recipient to donor BSA or body weight, kidney volume to recipient BSA, and kidney weight to recipient weight, on transplant outcomes.[153–158] Several caveats must be borne in mind when interpreting these data: BSA is not always proportional to kidney weight, and two kidneys of the same size may differ in nephron number. The evidence, however, despite the variability in methods, appears to be fairly consistent that small kidneys or kidneys from small donors transplanted into larger recipients tend to fare worse, supporting a role for nephron "dosing" in transplantation.[153–158]

As with most clinical questions, a long duration of follow-up is necessary when looking for out-comes that may take many years to manifest. Giral et al. previously published a cohort of renal allograft recipients, with a mean of 32 months of follow-up, in whom they found no impact of graft weight on short-term graft survival.[159] In their longer-term study, however, they used a donor kidney weight to recipient body weight (DKW/RBW) ratio of 2.3 to stratify recipients into two groups.[160] The low DKW/RBW group showed a greater adaptive increase in GFR during the first 6 months post-transplant, which remained stable for 7 years but then declined faster after 7 years compared to the high DKW/RBW group. This observation suggests initial hyperfiltration in the smaller kidneys, which could not be sustained after 7 years, likely due to on-going nephron loss, as reflected in more proteinuria, more antihypertensive drug use, a greater degree of glomerulosclerosis, and a 55% increased risk for transplant failure by 2 years in the low DKW/RBW group. The authors conclude that incompatibility between graft and recipient weight is an independent predictor of long-term graft survival. These data strongly support the contention that nephron "dose", relative to the recipient's needs, should be an important consideration in organ allocation.

Strategies for Optimization of Nephron Number

Evidence is emerging that clinically feasible interventions, at a critical period of nephron development, can rescue nephron number and impact later life blood pressure. In rats, adequate postnatal nutrition, achieved by cross-fostering growth-restricted pups onto normal lactating females at birth, was found to restore nephron number and abrogate development of subsequent hypertension.[73] Similarly, supplementation of maternal low-protein diet with glycine, urea, or alanine during gestation normalized nephron number in all rat offspring, although blood pressure was only normalized in those supplemented with glycine.[71] Postnatal hypernutrition in normal rats was found to increase nephron number by 20%, but these rats went on to develop hypertension and glomerulosclerosis with age, likely as a result of obesity.[72] Vitamin A deficiency has been shown to reduce nephron number in a dose-dependent manner, but encouragingly a single dose of retinoic acid, administered during early nephrogenesis, was enough to restore

nephron numbers to levels of control rats in pups exposed to a low-protein diet *in utero*.[30,161] Interestingly, administration of ouabain was also found to abrogate the effect of serum starvation and low-protein diet on nephron development *in vitro* and *in vivo* again in rats.[162] Although still preliminary, taken together, these studies suggest possible mechanisms whereby nephron numbers could be rescued if at-risk fetuses were identified early enough. Likewise, avoidance or judicious use of drugs during pregnancy, that are known to impact kidney development as described above, are another means to optimize fetal nephron number.[21–30,32–34,36,163–165]

CONCLUSION

The idea that low nephron number may have a long-term impact on an individual's later life risk of hypertension and renal disease has now entered the main stream. Until we learn more about developmental programming in nephrology, LBW should be used as the most useful current clinical surrogate for low nephron number and inborn risk of hypertension and renal disease. It is not surprising that nephron number and LBW are not the whole story, however. Other factors such as glomerular size, expression of sodium transporters, vascular reactivity, and high birth weight are also all important contributors and deserve more investigation. The demonstration that nephron numbers can be restored with timely intervention in experimental models points to plasticity within the system, making identification of individuals at risk and development of therapeutic tools even more urgent and compelling. Until such tools are developed, current evidence calls for optimization of perinatal care and early childhood nutrition as important strategies to help stem the growing epidemics of renal and cardiovascular disease in future generations.

REFERENCES

1. Brenner BM, Garcia DL, Anderson S. Glomeruli and blood pressure. Less of one, more the other? Am J Hypertens 1988;1:335–47.

2. Vehaskari VM, Aviles DH, Manning J. Prenatal programming of adult hypertension in the rat. Kidney Int 2001;59:238–45. doi:10.1046/j.1523-1755.2001.00484.x

3. Baum M. Role of the kidney in the prenatal and early postnatal programming of hypertension. Am J Physiol Renal Physiol 2010;298:F235–47. doi:10.1152/ajprenal.00288.2009

4. Bhathena DB, Julian BA, McMorrow RG, Baehler RW. Focal sclerosis of hypertrophied glomeruli in solitary functioning kidneys of humans. Am J Kidney Dis 1985;5:226–32.

5. Hoy WE, Hughson MD, Bertram JF, Douglas-Denton R, Amann K. Nephron number, hypertension, renal disease, and renal failure. J Am Soc Nephrol 2005;16:2557–64. doi:10.1681/ASN.2005020172

6. Keller G, Zimmer G, Mall G, Ritz E, Amann K. Nephron number in patients with primary hypertension. N Engl J Med 2003;348:101–8. doi:10.1056/NEJMoa020549

7. McMillen IC, Robinson JS. Developmental origins of the metabolic syndrome: Prediction, plasticity, and programming. Physiol Rev 2005;85:571–633. doi:10.1152/physrev.00053.2003

8. Schreuder MF, Langemeijer ME, Bokenkamp A, Delemarre-Van de Waal HA, Van Wijk JA. Hypertension and microalbuminuria in children with congenital solitary kidneys. J Paediatr Child Health 2008;44:363–8. doi:10.1111/j.1440-1754.2008.01315.x

9. McNamara BJ, Diouf B, Douglas-Denton RN, Hughson MD, Hoy WE, Bertram JF. A comparison of nephron number, glomerular volume and kidney weight in Senegalese Africans and African Americans. Nephrol Dial Transplant 2010;25:1514–20. doi:10.1093/ndt/gfq030

10. Hinchliffe SA, Sargent PH, Howard CV, Chan YF, van Velzen D. Human intrauterine renal growth expressed in absolute number of glomeruli assessed by the disector method and cavalieri principle. Lab Invest 1991;64:777–84.

11. Hughson M, Farris AB, Douglas-Denton R, Hoy WE, Bertram JF. Glomerular number and size in autopsy kidneys: The relationship to birth weight. Kidney Int 2003;63:2113–22. doi:10.1046/j.1523-1755.2003.00018.x

12. Manalich R, Reyes L, Herrera M, Melendi C, Fundora I. Relationship between weight at birth and the number and size of renal glomeruli in humans: A histomorphometric study. Kidney Int 2000;58:770–3. doi:10.1046/j.1523-1755.2000.00225.x

13. McNamara BJ, Diouf B, Hughson MD, Douglas-Denton RN, Hoy WE, Bertram JF. Renal pathology, glomerular number and volume in a West African urban community. Nephrol Dial Transplant 2008;23:2576–85. doi:10.1093/ndt/gfn039

14. McNamara BJ, Diouf B, Hughson MD, Hoy WE, Bertram JF. Associations between age, body size and nephron number with individual glomerular volumes in urban West African males. Nephrol Dial Transplant 2009;24:1500–6. doi:10.1093/ndt/gfn636

15. 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. doi:10.1002/ar.1092320205

16. Rodriguez MM, Gomez AH, Abitbol CL, Chandar JJ, Duara S, Zilleruelo GE. Histomorphometric analysis of postnatal glomerulogenesis in extremely preterm infants. Pediatr Dev Pathol 2004;7:17–25. doi:10.1007/s10024-003-3029-2

17. Zimanyi MA, Hoy WE, Douglas-Denton RN, Hughson MD, Holden LM, Bertram JF. Nephron number and individual glomerular volumes in male Caucasian and African American subjects. Nephrol Dial Transplant 2009;24:2428–33. doi:10.1093/ndt/gfp116

18. Hinchliffe SA, Howard CV, Lynch MR, Sargent PH, Judd BA, van Velzen D. Renal developmental arrest in sudden infant death syndrome. Pediatr Pathol 1993;13:333–43. doi:10.3109/15513819309048221

19. Gubhaju L, Sutherland MR, Yoder BA, Zulli A, Bertram JF, Black MJ. Is nephrogenesis affected by preterm birth? Studies in a non-human primate model. Am J Physiol Renal Physiol 2009;297:F1668–77. doi:10.1152/ajprenal.00163.2009

20. Villar-Martini VC, Carvalho JJ, Neves MF, Aguila MB, Mandarim-de-Lacerda CA. Hypertension and kidney alterations in rat offspring from low protein pregnancies. J Hypertens Suppl 2009;27:S47–51. doi:10.1097/01.hjh.0000358838.71675.5e

21. 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:R568–74. doi:10.1152/ajpregu.90316.2008

22. Amri K, Freund N, Van Huyen JP, Merlet-Benichou C, Lelievre-Pegorier M. Altered nephrogenesis due to maternal diabetes is associated with increased expression of IGF-II/mannose-6-phosphate receptor in the fetal kidney. Diabetes 2001;50:1069–75. doi:10.2337/diabetes.50.5.1069

23. Celsi G, Kistner A, Aizman R, et al. Prenatal dexamethasone causes oligonephronia, sodium retention, and higher blood pressure in the offspring. Pediatr Res 1998;44:317–22. doi:10.1203/00006450-199809000-00009

24. Gilbert T, Cibert C, Moreau E, Geraud G, Merlet-Benichou C. Early defect in branching morpho-genesis of the ureteric bud in induced nephron deficit. Kidney Int 1996;50:783–95. doi:10.1038/ki.1996.377

25. Harrison M, Langley-Evans SC. Intergenerational programming of impaired nephrogenesis and hypertension in rats following maternal protein restriction during pregnancy. Br J Nutr 2009;101:1020-30. doi:10.1017/S0007114508057607

26. Komhoff M, Wang JL, Cheng HF, et al. Cyclooxygenase-2-selective inhibitors impair glomerulogenesis and renal cortical development. Kidney Int 2000;57:414–22.

27. Langley-Evans SC. Nutritional programming of disease: Unravelling the mechanism. J Anat 2009;215:36–51. doi:10.1111/j.1469-7580.2008.00977.x

28. Lisle SJ, Lewis RM, Petry CJ, Ozanne SE, Hales CN, Forhead AJ. Effect of maternal iron restriction during pregnancy on renal morphology in the adult rat offspring. Br J Nutr 2003;90:33–9. doi:10.1079/BJN2003881

29. Magaton A, Gil FZ, Casarini DE, Cavanal Mde F, Gomes GN. Maternal diabetes mellitus – early consequences for the offspring. Pediatr Nephrol 2007;22:37–43. doi:10.1007/s00467-006-0282-4

30. Merlet-Benichou C, Vilar J, Lelievre-Pegorier M, Gilbert T. Role of retinoids in renal development: Pathophysiological implication. Curr Opin Nephrol Hypertens 1999;8:39–43. doi:10.1097/00041552-199901000-00007

31. Merlet-Benichou C, Gilbert T, Vilar J, Moreau E, Freund N, Lelievre-Pegorier M. Nephron number: Variability is the rule. Causes and consequences. Lab Invest 1999;79:515–27.

32. Nathanson S, Moreau E, Merlet-Benichou C, Gilbert T. *In utero* and *in vitro* exposure to beta-lactams impair kidney development in the rat. J Am Soc Nephrol 2000;11:874–84.

33. Tendron-Franzin A, Gouyon JB, Guignard JP, et al. Long-term effects of in utero exposure to cyclo-sporin a on renal function in the rabbit. J Am Soc Nephrol 2004;15:2687–93. doi:10.1097/01.ASN.0000139069.59466.D8

34. Welham SJ, Riley PR, Wade A, Hubank M, Woolf AS. Maternal diet programs embryonic kidney gene expression. Physiol Genomics 2005;22:48–56. doi:10.1152/physiolgenomics.00167.2004

35. Moritz KM, Dodic M, Wintour EM. Kidney development and the fetal programming of adult disease. Bioessays 2003;25:212–20. doi:10.1002/bies.10240

36. Woods LL, Ingelfinger JR, Nyengaard JR, Rasch R. Maternal protein restriction suppresses the new-

born renin-angiotensin system and programs adult hypertension in rats. Pediatr Res 2001;49:460–7. doi:10.1203/00006450-200104000-00005

37. 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. doi:10.1016/j.ejogrb.2004.03.007

38. Tierney-Gumaer R, Reifsnider E. Risk factors for low birth weight infants of Hispanic, African American, and white women in Bexar County, Texas. Public Health Nurs 2008;25:390–400. doi:10.1111/j.1525-1446.2008.00723.x

39. Fall C. Maternal nutrition: Effects on health in the next generation. Indian J Med Res 2009;130:593–9.

40. Blumenshine P, Egerter S, Barclay CJ, Cubbin C, Braveman PA. Socioeconomic disparities in adverse birth outcomes: A systematic review. Am J Prev Med 2010;39:263–72. doi:10.1016/j.amepre.2010.05.012

41. Collins JW, Rankin KM, David RJ. Low birth weight across generations: The effect of economic environment. Matern Child Health J 2011;15:438–45. doi:10.1007/s10995-010-0603-x

42. Hinchliffe SA, Lynch MR, Sargent PH, Howard CV, Van Velzen D. The effect of intrauterine growth retardation on the development of renal nephrons. Br J Obstet Gynaecol 1992;99:296–301. doi:10.1111/j.1471-0528.1992.tb13726.x

43. Hoy WE, Bertram JF, Denton RD, Zimanyi M, Samuel T, Hughson MD. Nephron number, glomerular volume, renal disease and hypertension. Curr Opin Nephrol Hypertens 2008;17:258–65. doi:10.1097/MNH.0b013e3282f9b1a5

44. Nelson RG, Morgenstern H, Bennett PH. Birth weight and renal disease in Pima Indians with type 2 diabetes mellitus. Am J Epidemiol 1998;148:650–6. doi:10.1093/aje/148.7.650

45. Nelson RG, Morgenstern H, Bennett PH. Intrauterine diabetes exposure and the risk of renal disease in diabetic Pima Indians. Diabetes 1998;47:1489–93. doi:10.2337/diabetes.47.9.1489

46. Amri K, Freund N, Vilar J, Merlet-Benichou C, Lelievre-Pegorier M. Adverse effects of hyperglycemia on kidney development in rats: *In vivo* and *in vitro* studies. Diabetes 1999;48:2240–5. doi:10.2337/diabetes.48.11.2240

47. Jones SE, Bilous RW, Flyvbjerg A, Marshall SM. Intra-uterine environment influences glomerular number and the acute renal adaptation to experimental diabetes. Diabetologia 2001;44:721–8. doi:10.1007/s001250051681

48. Tran S, Chen YW, Chenier I, et al. Maternal diabetes modulates renal morphogenesis in offspring. J Am Soc Nephrol 2008;19:943–52. doi:10.1681/ASN.2007080864

49. Moritz KM, Wintour EM, Black MJ, Bertram JF, Caruana G. Factors influencing mammalian kidney development: Implications for health in adult life. Adv Anat Embryol Cell Biol 2008;196:1–78.

50. 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;14:2767–74. doi:10.1097/01.ASN.0000094082.11026.EE

51. 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;18:1915–21. doi:10.1681/ASN.2006101107

52. 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;19:2027–34. doi:10.1681/ASN.2007101098

53. Weber S, Moriniere V, Knuppel T, et al. Prevalence of mutations in renal developmental genes in children with renal hypodysplasia: Results of the escape study. J Am Soc Nephrol 2006;17:2864–70. doi:10.1681/ASN.2006030277

54. Fulladosa X, Moreso F, Narvaez JA, Grinyo JM, Seron D. Estimation of total glomerular number in stable renal transplants. J Am Soc Nephrol 2003;14:2662–8. doi:10.1097/01.ASN.0000088025.33462.B0

55. Gilbert JS, Lang AL, Grant AR, Nijland MJ. Maternal nutrient restriction in sheep: Hypertension and decreased nephron number in offspring at 9 months of age. J Physiol 2005;565:137–47. doi:10.1113/jphysiol.2005.084202

56. Jones SE, Nyengaard JR, Flyvbjerg A, Bilous RW, Marshall SM. Birth weight has no influence on glomerular number and volume. Pediatr Nephrol 2001;16:340–5. doi:10.1007/s004670000559

57. Hoy WE, Douglas-Denton RN, Hughson MD, Cass A, Johnson K, Bertram JF. A stereological study of glomerular number and volume: Preliminary findings in a multiracial study of kidneys at autopsy. Kidney Int Suppl 2003:S31–7. doi:10.1046/j.1523-1755.63.s83.8.x

58. Hoy WE, Hughson MD, Singh GR, Douglas-Denton R, Bertram JF. Reduced nephron number and glomerulomegaly in Australian Aborigines: A group at high risk for renal disease and hypertension. Kidney Int 2006;70:104–10. doi:10.1038/sj.ki.5000397

59. Elia M, Betts P, Jackson DM, Mulligan J. Fetal programming of body dimensions and percentage body fat measured in prepubertal children with a 4-component model of body composition, dual-energy X-ray absorptiometry, deuterium dilution, densitometry, and skinfold thicknesses. Am J Clin Nutr 2007;86:618–24.

60. Spencer J, Wang Z, Hoy W. Low birth weight and reduced renal volume in Aboriginal children. Am J Kidney Dis 2001;37:915–20. doi:10.1016/S0272-6386(05)80006-X

61. 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;23:1309–15. doi:10.1007/s00467-008-0824-z

62. Keijzer-Veen MG, Devos AS, Meradji M, Dekker FW, Nauta J, van der Heijden BJ. Reduced renal length and volume 20 years after very preterm birth. Pediatr Nephrol 2010;25:499–507. doi:10.1007/s00467-009-1371-y

63. Kett MM, Bertram JF. Nephron endowment and blood pressure: What do we really know? Curr Hypertens Rep 2004;6:133–9. doi:10.1007/s11906-004-0089-2

64. Moritz KM, Wintour EM, Dodic M. Fetal uni-nephrectomy leads to postnatal hypertension and compromised renal function. Hypertension 2002;39:1071–6. doi:10.1161/01.HYP.0000019131.77075.54

65. Woods LL, Weeks DA, Rasch R. Hypertension after neonatal uninephrectomy in rats precedes glomerular damage. Hypertension 2001;38:337–42.

66. 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;27:386-96. doi:10.1097/HJH.0b013e32831bc778

67. Nyengaard JR. Number and dimensions of rat glomerular capillaries in normal development and after nephrectomy. Kidney Int 1993;43:1049–57. doi:10.1038/ki.1993.147

68. Ruta LA, Dickinson H, Thomas MC, Denton KM, Anderson WP, Kett MM. High-salt diet reveals the hypertensive and renal effects of reduced nephron endowment. Am J Physiol Renal Physiol 2010;298:F1384–92. doi:10.1152/ajprenal.00049.2010

69. Nenov VD, Taal MW, Sakharova OV, Brenner BM. Multi-hit nature of chronic renal disease. Curr Opin Nephrol Hypertens 2000;9:85–97. doi:10.1097/00041552-200003000-00001

70. Hughson MD, Douglas-Denton R, Bertram JF, Hoy WE. Hypertension, glomerular number, and birth weight in African Americans and white subjects in the southeastern United States. Kidney Int 2006;69:671–8. doi:10.1038/sj.ki.5000041

71. Langley-Evans S, Langley-Evans A, Marchand M. Nutritional programming of blood pressure and renal morphology. Arch Physiol Biochem 2003;111:8–16. doi:10.1076/apab.111.1.8.15136

72. 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:F1944–9. doi:10.1152/ajprenal.00141.2007

73. Wlodek ME, Mibus A, Tan A, Siebel AL, Owens JA, Moritz KM. Normal lactational environment restores nephron endowment and prevents hypertension after placental restriction in the rat. J Am Soc Nephrol 2007;18:1688–96. doi:10.1681/ASN.2007010015

74. Alexander BT. Placental insufficiency leads to development of hypertension in growth-restricted offspring. Hypertension 2003;41:457–62. doi:10.1161/01.HYP.0000053448.95913.3D

75. Forrester TE, Wilks RJ, Bennett FI, et al. Fetal growth and cardiovascular risk factors in Jamaican schoolchildren. Br Med J 1996;312:156–60.

76. Law CM, Shiell AW. Is blood pressure inversely related to birth weight? The strength of evidence from a systematic review of the literature. J Hypertens 1996;14:935–41. doi:10.1097/00004872-199608000-00002

77. 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;53:264–8. doi:10.1136/jech.53.5.264

78. Longo-Mbenza B, Ngiyulu R, Bayekula M, et al. Low birth weight and risk of hypertension in African school children. J Cardiovasc Risk 1999;6:311–4.

79. 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;155:601–7. doi:10.1530/eje.1.02265

80. 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;16:2762–8. doi:10.1681/ASN.2004090783

81. 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;68:731-40. doi:10.1111/j.1523-1755.2005.00451.x

82. Keijzer-Veen MG, Dulger A, Dekker FW, Nauta J, van der Heijden BJ. Very preterm birth is a risk factor for increased systolic blood pressure at a young adult age. Pediatr Nephrol 2010;25:509–16. doi:10.1007/s00467-009-1373-9

83. 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;115:2931–8. doi:10.1161/CIRCULATIONAHA.106.674812

84. Falkner B, Hulman S, Kushner H. Effect of birth weight on blood pressure and body size in early adolescence. Hypertension 2004;43:203–7. doi:10.1161/01.HYP.0000109322.72948.24

85. 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;360:659–65. doi:10.1016/S0140-6736(02)09834-3

86. Muhle A, Muhle C, Amann K, et al. No juvenile arterial hypertension in sheep multiples despite reduced nephron numbers. Pediatr Nephrol 2010;25:1653–61. doi:10.1007/s00467-010-1512-3

87. 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;17:2576–81. doi:10.1681/ASN.2005090898

88. Luyckx VA, Brenner BM. The clinical importance of nephron mass. J Am Soc Nephrol 2010;21:898–910. doi:10.1681/ASN.2009121248

89. de Boer MP, Ijzerman RG, de Jongh RT, et al. Birth weight relates to salt sensitivity of blood pressure in healthy adults. Hypertension 2008;51:928–32. doi:10.1161/HYPERTENSIONAHA.107.101881

90. Simonetti GD, Raio L, Surbek D, Nelle M, Frey FJ, Mohaupt MG. Salt sensitivity of children with low birth weight. Hypertension 2008;52:625–30. doi:10.1161/HYPERTENSIONAHA.108.114983

91. Dagan A, Gattineni J, Cook V, Baum M. Prenatal programming of rat proximal tubule Na+/H+ exchanger by dexamethasone. Am J Physiol Regul Integr Comp Physiol 2007;292:R1230–5. doi:10.1152/ajpregu.00669.2006

92. Manning J, Beutler K, Knepper MA, Vehaskari VM. Upregulation of renal bsc1 and tsc in prenatally programmed hypertension. Am J Physiol Renal Physiol 2002;283:F202–6.

93. Vehaskari VM, Stewart T, Lafont D, Soyez C, Seth D, Manning J. Kidney angiotensin and angiotensin receptor expression in prenatally programmed hypertension. Am J Physiol Renal Physiol 2004;287:F262–7. doi:10.1152/ajprenal.00055.2004

94. Alwasel SH, Kaleem I, Sahajpal V, Ashton N. Maternal protein restriction reduces angiotensin II at(1) and at(2) receptor expression in the fetal rat kidney. Kidney Blood Press Res 2010;33:251–9. doi:10.1159/000317739

95. Dagan A, Gattineni J, Habib S, Baum M. Effect of prenatal dexamethasone on postnatal serum and urinary angiotensin II levels. Am J Hypertens 2010;23:420–4. doi:10.1038/ajh.2009.274

96. Salgado CM, Jardim PC, Teles FB, Nunes MC. Low birth weight as a marker of changes in ambulatory blood pressure monitoring. Arq Bras Cardiol 2009;92:107–21.

97. Dagan A, Habib S, Gattineni J, Dwarakanath V, Baum M. Prenatal programming of rat thick ascending limb chloride transport by low-protein diet and dexamethasone. Am J Physiol Regul Integr Comp Physiol 2009;297:R93–9. doi:10.1152/ajpregu.91006.2008

98. Dagan A, Kwon HM, Dwarakanath V, Baum M. Effect of renal denervation on prenatal programming of hypertension and renal tubular transporter abundance. Am J Physiol Renal Physiol 2008;295:F29–34. doi:10.1152/ajprenal.00123.2008

99. Dotsch J. Renal and extrarenal mechanisms of perinatal programming after intrauterine growth restriction. Hypertens Res 2009;32:238–41. doi:10.1038/hr.2009.4

100. Franco MC, Christofalo DM, Sawaya AL, Ajzen SA, Sesso R. 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. doi:10.1161/01.HYP.0000223446.49596.3a

101. Franco Mdo C, Arruda RM, Fortes ZB, et al. Severe nutritional restriction in pregnant rats aggravates hypertension, altered vascular reactivity, and renal development in spontaneously hypertensive rats offspring. J Cardiovasc Pharmacol 2002;39:369–77. doi:10.1097/00005344-200203000-00008

102. 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. doi:10.1042/CS20070113

103. Maahs DM, Snively BM, Beyer J, et al. Birth weight [corrected] and elevated albumin to creatinine ratio in youth with diabetes: The search for diabetes in youth study. Pediatr Nephrol 2008;23:2255–60. doi:10.1007/s00467-008-0921-z

104. Hoy WE, Rees M, Kile E, et al. Low birthweight and renal disease in Australian aborigines. Lancet 1998; 352:1826–7. doi:10.1016/S0140-6736(05)79888-3

105. Hoy WE, Rees M, Kile E, Mathews JD, Wang Z. A new dimension to the barker hypothesis: Low birthweight and susceptibility to renal disease. Kidney Int 1999;56:1072–7. doi:10.1046/j.1523-1755.1999.00633.x

106. Hoy WE, Wang Z, VanBuynder P, Baker PR, McDonald SM, Mathews JD. The natural history of renal disease in Australian Aborigines. Part 2. Albuminuria predicts natural death and renal failure. Kidney Int 2001;60:249–56. doi:10.1046/j.1523-1755.2001.00793.x

107. Hoy WE, Wang Z, VanBuynder P, Baker PR, Mathews JD. The natural history of renal disease in Australian Aborigines. Part 1. Changes in albuminuria and glomerular filtration rate over time. Kidney Int 2001;60:243–8. doi:10.1046/j.1523-1755.2001.00792.x

108. Jones SE, White KE, Flyvbjerg A, Marshall SM. The effect of intrauterine environment and low glomerular number on the histological changes in diabetic glomerulosclerosis. Diabetologia 2006;49: 191–9. doi:10.1007/s00125-005-0052-z

109. Schreuder MF, Wilhelm AJ, Bokenkamp A, Timmermans SM, Delemarre-van de Waal HA, van Wijk JA. Impact of gestational age and birth weight on amikacin clearance on day 1 of life. Clin J Am Soc Nephrol 2009;4:1774–8. doi:10.2215/CJN.02230409

110. Rodriguez-Soriano J, Aguirre M, Oliveros R, Vallo A. Long-term renal follow-up of extremely low birth weight infants. Pediatr Nephrol 2005;20:579–84. doi:10.1007/s00467-005-1828-6

111. 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;51:925–32. doi:10.1053/j.ajkd.2008.02.305

112. Ingelfinger JR. Weight for gestational age as a baseline predictor of kidney function in adulthood. Am J Kidney Dis 2008;51:1–4. doi:10.1053/j.ajkd.2007.11.004

113. 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;16:2471–6. doi:10.1681/ASN.2004030210

114. 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; 59:2631–6. doi:10.2337/db10-0419

115. 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;50:542–51. doi:10.1053/j.ajkd.2007.06.015

116. 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;54:248–61. doi:10.1053/j.ajkd.2008.12.042

117. Li S, Chen SC, Shlipak M, et al. Low birth weight is associated with chronic kidney disease only in men. Kidney Int 2008;73:637–42. doi:10.1038/sj.ki.5002747

118. Grigore D, Ojeda NB, Alexander BT. Sex differences in the fetal programming of hypertension. Gend Med 2008;5 Suppl A:S121–32.

119. Vikse BE, Irgens LM, Leivestad T, Hallan S, Iversen BM. Low birth weight increases risk for end-stage renal disease. J Am Soc Nephrol 2008;19:151–7. doi:10.1681/ASN.2007020252

120. Lackland DT, Bendall HE, Osmond C, Egan BM, Barker DJ. Low birth weights contribute to high rates of early-onset chronic renal failure in the southeastern United States. Arch Intern Med 2000; 160:1472–6. doi:10.1001/archinte.160.10.1472

121. Hodgin JB, Rasoulpour M, Markowitz GS, D'Agati VD. Very low birth weight is a risk factor for secondary focal segmental glomerulosclerosis. Clin J Am Soc Nephrol 2009;4:71–6. doi:10.2215/CJN.01700408

122. Duncan RC, Bass PS, Garrett PJ, Dathan JR. Weight at birth and other factors influencing progression of idiopathic membranous nephronpathy. Nephrol Dial Transplant 1994;9:875.

123. Na YW, Yang HJ, Choi JH, et al. Effect of intrauterine growth retardation on the progression of nephrotic syndrome. Am J Nephrol 2002;22: 463–7. doi:10.1159/000065275

124. Teeninga N, Schreuder MF, Bokenkamp A, Delemarre-van de Waal HA, van Wijk JA. Influence of low birth weight on minimal change nephrotic syndrome in children, including a meta-analysis. Nephrol Dial Transplant 2008;23:1615–20. doi:10.1093/ndt/gfm829

125. Zidar N, Avgustin Cavic M, Kenda RB, Ferluga D. Unfavorable course of minimal change nephrotic syndrome in children with intrauterine growth retardation. Kidney Int 1998;54:1320–3. doi:10.1046/j.1523-1755.1998.00121.x

126. 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;32:287–95. doi:10.1159/000319045

127. Hershkovitz D, Burbea Z, Skorecki K, Brenner BM. Fetal programming of adult kidney disease: Cellular and molecular mechanisms. Clin J Am Soc Nephrol 2007;2:334–42. doi:10.2215/CJN. 03291006

128. Barker DJ, Osmond C, Forsen TJ, Kajantie E, Eriksson JG. Trajectories of growth among children who have coronary events as adults. N Engl J Med 2005;353:1802–9. doi:10.1056/NEJMoa044160

129. Cameron N, Demerath EW. Critical periods in human growth and their relationship to diseases of aging. Am J Phys Anthropol 2002;Suppl 35:159–84. doi:10.1002/ajpa.10183

130. Bhargava SK, Sachdev HS, Fall CH, et al. Relation of serial changes in childhood body-mass index to impaired glucose tolerance in young adulthood. N Engl J Med 2004;350:865–75. doi:10.1056/NEJMoa035698

131. Singhal A, Cole TJ, Fewtrell M, Deanfield J, Lucas A. Is slower early growth beneficial for long-term cardiovascular health? Circulation 2004;109:1108–13. doi:10.1161/01.CIR.0000118500.23649.DF

132. Hales CN, Barker DJ. The thrifty phenotype hypothesis. Br Med Bull 2001;60:5–20. doi:10.1093/bmb/60.1.5

133. Luyckx VA, Compston CA, Simmen T, Mueller TF. Accelerated senescence in kidneys of low-birth-weight rats after catch-up growth. Am J Physiol Renal Physiol 2009;297:F1697–705. doi:10.1152/ajprenal.00462.2009

134. Ozanne SE, Hales CN. Lifespan: Catch-up growth and obesity in male mice. Nature 2004;427:411–2. doi:10.1038/427411b

135. Tarry-Adkins JL, Martin-Gronert MS, Chen JH, Cripps RL, Ozanne SE. Maternal diet influences DNA damage, aortic telomere length, oxidative stress, and antioxidant defense capacity in rats. FASEB J 2008;22:2037–44. doi:10.1096/fj.07-099523

136. Tarry-Adkins JL, Ozanne SE, Norden A, Cherif H, Hales CN. 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: F509–16. doi:10.1152/ajprenal.00215.2005

137. Akkad A, Hastings R, Konje JC, Bell SC, Thurston H, Williams B. Telomere length in small-for-gestational-age babies. BJOG 2006;113:318–23. doi:10.1111/j.1471-0528.2005.00839.x

138. Hales CN, Ozanne SE. The dangerous road of catch-up growth. J Physiol 2003;547:5–10. doi:10.1113/jphysiol.2002.024406

139. Mohn A, Chiavaroli V, Cerruto M, et al. Increased oxidative stress in prepubertal children born small for gestational age. J Clin Endocrinol Metab 2007;92:1372–8. doi:10.1210/jc.2006-1344

140. 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;85:845–52.

141. Hakim RM, Goldszer RC, Brenner BM. Hypertension and proteinuria: Long-term sequelae of uninephrectomy in humans. Kidney Int 1984;25: 930–6. doi:10.1038/ki.1984.112

142. Flanigan WJ, Burns RO, Takacs FJ, Merril JP. Serial studies of glomerular filtration rate and renal plasma flow in kidney transplant donors, identical twins, and allograft recipients. Am J Surg 1968;116: 788–94. doi:10.1016/0002-9610(68)90370-X

143. Ibrahim HN, Foley R, Tan L, et al. Long-term consequences of kidney donation. N Engl J Med 2009;360:459–69. doi:10.1056/NEJMoa0804883

144. Kasiske BL, Ma JZ, Louis TA, Swan SK. Long-term effects of reduced renal mass in humans. Kidney Int 1995;48:814–9. doi:10.1038/ki.1995.355

145. Goldfarb DA, Matin SF, Braun WE, et al. Renal outcome 25 years after donor nephrectomy. J Urol 2001;166:2043–7. doi:10.1016/S0022-5347(05)65502-4

146. Storsley LJ, Young A, Rush DN, et al. Long-term medical outcomes among Aboriginal living kidney donors. Transplantation 2010;90:401–6. doi:10.1097/TP.0b013e3181e6e79b

147. Lentine KL, Schnitzler MA, Xiao H, et al. Racial variation in medical outcomes among living kidney donors. N Engl J Med 2010;363:724–32. doi:10.1056/NEJMoa1000950

148. Gibney EM, Parikh CR, Garg AX. Age, gender, race, and associations with kidney failure following living kidney donation. Transplant Proc 2008;40:1337–40. doi:10.1016/j.transproceed.2008.03.104

149. Brenner BM, Cohen RA, Milford EL. In renal transplantation, one size may not fit all. J Am Soc Nephrol 1992;3:162–9.

150. Azuma H, Nadeau K, Mackenzie HS, Brenner BM, Tilney NL. Nephron mass modulates the hemodynamic, cellular and molecular response of the rat renal allograft. Transplantation 1997;63:519–28. doi:10.1097/00007890-199702270-00006

151. Mackenzie HS, Azuma H, Troy JL, Rennke HG, Tilney NL, Brenner BM. Augmenting kidney mass at transplantation abrogates chronic renal allograft injury in rats. Proc Assoc Am Phys 1996;108:127–33

152. Szabo AJ, Muller V, Chen GF, Samsell LJ, Erdely A, Baylis C. 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;23:2492–5. doi:10.1093/ndt/gfn112

153. Douverny JB, Baptista-Silva JC, Pestana JO, Sesso R. Importance of renal mass on graft function outcome after 12 months of living donor kidney transplantation. Nephrol Dial Transplant 2007;22:3646–51. doi:10.1093/ndt/gfm487

154. el-Agroudy AE, Hassan NA, Bakr MA, Foda MA, Shokeir AA, Shehab el-Dein AB. Effect of donor/recipient body weight mismatch on patient and graft outcome in living-donor kidney transplantation. Am J Nephrol 2003;23:294–9. doi:10.1159/000072819

155. Gaston RS, Hudson SL, Julian BA, et al. Impact of donor/recipient size matching on outcomes in renal transplantation. Transplantation 1996;61:383–8. doi:10.1097/00007890-199602150-00010

156. Kasiske BL, Snyder JJ, Gilbertson D. Inadequate donor size in cadaver kidney transplantation. J Am Soc Nephrol 2002;13:2152–9. doi:10.1097/01.ASN.0000024564.22119.3D

157. Kim YS, Moon JI, Kim DK, Kim SI, Park K. Ratio of donor kidney weight to recipient bodyweight as an index of graft function. Lancet 2001;357:1180–1. doi:10.1016/S0140-6736(00)04377-4

158. Moreso F, Seron D, Anunciada AI, et al. Recipient body surface area as a predictor of post-transplant renal allograft evolution. Transplantation 1998;65:671–6. doi:10.1097/00007890-199803150-00012

159. Giral M, Nguyen JM, Karam G, et al. Impact of graft mass on the clinical outcome of kidney transplants. J Am Soc Nephrol 2005;16:261–8. doi:10.1681/ASN.2004030209

160. Giral M, Foucher Y, Karam G, et al. Kidney and recipient weight incompatibility reduces long-term graft survival. J Am Soc Nephrol 2010;21:1022–9. doi:10.1681/ASN.2009121296

161. Makrakis J, Zimanyi MA, Black MJ. Retinoic acid enhances nephron endowment in rats exposed to maternal protein restriction. Pediatr Nephrol 2007;22:1861–7. doi:10.1007/s00467-007-0572-5

162. Li J, Khodus G, Kruusmagi M, et al. Ouabain protects against adverse developmental programming of the kidney. Nat Commun 2010;1:42. doi:10.1038/ncomms1043

163. Bertram C, Trowern AR, Copin N, Jackson AA, Whorwood CB. 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;142:2841–53. doi:10.1210/en.142.7.2841

164. Merlet-Benichou C. Influence of fetal environment on kidney development. Int J Dev Biol 1999;43:453–6.

165. Wintour EM, Moritz KM, Johnson K, Ricardo S, Samuel CS, Dodic M. Reduced nephron number in adult sheep, hypertensive as a result of prenatal glucocorticoid treatment. J Physiol 2003;549:929–35. doi:10.1113/jphysiol.2003.042408