Effect of fetal and child health on kidney development and long-term risk of hypertension and kidney disease

Valerie A Luyckx, John F Bertram, Barry M Brenner, Caroline Fall, Wendy E Hoy, Susan E Ozanne, Bjorn E Vikse

Developmental programming of non-communicable diseases is now an established paradigm. With respect to hypertension and kidney disease, adverse events experienced in utero can affect development of the fetal kidney and reduce final nephron number. Low birthweight and prematurity are the most consistent clinical surrogates for a low nephron number and are associated with increased risk of hypertension, proteinuria, and kidney disease in later life. Rapid weight gain in childhood or adolescence further compounds these risks. Low birthweight, prematurity, and rapid childhood weight gain should alert clinicians to an individual’s lifelong risk of hypertension and kidney disease, prompting education to minimise additional risk factors and ensuring follow-up. Birthweight and prematurity are affected substantially by maternal nutrition and health during pregnancy. The best maternal health and early childhood nutrition could, therefore, attenuate this programming cycle and reduce the global burden of hypertension and kidney disease in the future.

Introduction

Hypertension is now the leading risk factor for the global disease burden, and it is a major cause and effect of fetal and child health on kidney development and rapid childhood weight gain should alert clinicians to an individual’s lifelong risk of hypertension and kidney disease, prompting education to minimise additional risk factors and ensuring follow-up. Birthweight and prematurity are affected substantially by maternal nutrition and health during pregnancy. The best maternal health and early childhood nutrition could, therefore, attenuate this programming cycle and reduce the global burden of hypertension and kidney disease in the future.

Key messages

- Low birthweight and prematurity are risk factors for hypertension, proteinuria, and chronic kidney disease in later life
- Worldwide, low birthweight and prematurity occur in 15% and 9-6% of live births, respectively, suggesting a high proportion of the world’s children are at risk of hypertension and kidney disease
- Low birthweight and prematurity are associated with a congenital reduction in nephron number; in turn, small numbers of nephrons are associated with raised blood pressure and increased susceptibility to kidney disease [A: merged these two points, we prefer to list 5 key points]
- High birthweight, particularly as a result of exposure to maternal diabetes in utero, is associated with increased risk of proteinuria and kidney disease in later life
- Risk of low birthweight and prematurity is affected by maternal nutrition and health before and during pregnancy and by the mother’s own birthweight, indicating the intergenerational effects of programming
- Upward crossing of weight or body-mass-index percentiles in childhood or adolescence is associated with increased risk of high blood pressure, progression of renal disease, type 2 diabetes, obesity, and cardiovascular disease in later life; these effects can be independent of birthweight

Search strategy and selection criteria

We searched PubMed [A: between which dates? Month and year] with the terms “nephron number”, “nephron endowment”, “nephromass”, “nephrogenesis”, “birth weight”, “low birth weight”, “high birth weight”, “prematurity”, “preterm birth”, “developmental programming”, “developmental origins of adult health and disease”, “catch-up growth”, “growth restriction”, “SGA”, and “IUGR”, with other keywords including “kidney”, “kidney mass”, “kidney size”, “kidney volume”, “diabetes”, “gestational diabetes”, “cardiovascular disease”, “obesity”, “human”, “hypertension”, “hypertensive disorders in pregnancy”, “preeclampsia”, “vitamin A deficiency”, “maternal diet”, and “maternal nutrition”. We also looked at the reference lists of existing manuscripts, textbooks, and websites. Furthermore, we identified data, references, and links by searching the WHO, UNICEF, and Google Scholar websites [A: between which dates?] with the keywords “low birth weight”, “preeclampsia”, “gestational diabetes”, “maternal and newborn health”, “nutrition”, and “childhood obesity”. [A: did you impose any language restrictions?] We largely included publications from the past 5 years but also considered older seminal papers. Some references to experimental data were included when these were judged necessary to explain ideas strongly supporting the pathophysiology but not yet proven in man.

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development, and unhealthy childhood growth that all augment the risk of adult disease.14

Here, we describe how fetal and child health affect kidney development and risk of disease. We focus mainly on human studies but use experimental data when necessary to provide further insight.

**Effect of fetal development on the kidney**

About 25 years ago, Brenner and colleagues15 proposed that a congenital (developmentally programmed) decrease in nephron number could account for why some individuals are more susceptible to hypertension and renal injury than others. A kidney with fewer nephrons was postulated to have a diminished filtration surface area, resulting in limitation of sodium excretion leading to raised blood pressure and reduction of renal adaptive capacity in the setting of injury. This hypothesis provided a plausible link between a high prevalence of hypertension and renal disease in populations with an increased frequency of low birthweight, whereby low birthweight was expected to be associated with a lower number of nephrons (figure 1).* Consistent with this hypothesis, data from various experimental models confirm the association of low birthweight with later-life hypertension, mediated, in part, by acquisition of fewer nephrons in utero (the pathophysiological mechanisms affecting nephrogenesis are reviewed elsewhere).16 Similarly, in human beings, low birthweight is a risk factor for hypertension and chronic kidney disease.17

[A: please note that we prefer to avoid use of abbreviations, for clarity] Low birthweight is a marker of poor fetal growth. Risk factors for low birthweight vary in developed and developing countries but the global incidence is 15% a year [A: correct?], suggesting that many children are at risk of hypertension and kidney disease in later life (figure 2).18–22 [A: note that refs 11–15 are mentioned in the figure legend, I’ve renumbered] In view of the complexity and far-reaching effect of developmental programming, understanding the most proximal origins of hypertension and renal disease risk is crucial for expansion of public health strategies to reduce their global effect.3

Low birthweight is defined universally as a birthweight less than 2·5 kg, and high birthweight is classed as a birthweight heavier than 4·0 or 4·5 kg.23 [A: do you mean 4·0–4·5 kg? Why the two weights?] Other terms used to indicate neonatal size include intrauterine growth restriction (IUGR), small for gestational age, and salt sensitivity.

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*Figure 1: Factors affecting developmental programming of hypertension and kidney disease*

*Figure 2: Worldwide prevalence of factors affecting programming of renal disease, by UN region*

Error bars represent the range of prevalence, by region. *Excludes countries with 2005 gross domestic product of US$15,000 or higher, where vitamin A deficiency is presumed absent. *Obesity figures for North America and Europe are extrapolated from data for “developed countries”. Childhood obesity is defined as two or more SD from weight-for-height median. Data are pooled from references 11-15.

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**Notes:**

age, and high birthweight as children with a birthweight greater than 4–0·4–5 kg, including those who are large for gestational age. A premature infant—ie, who is born before 37 weeks of gestation—is generally low birthweight, which might be an appropriate weight for gestational age if growth occurred normally until birth, but could be small for gestational age if growth were restricted.26

Nephron number in children and adults
The total number of nephrons in the normal adult human kidney varies widely.27 The average number of nephrons per kidney was assumed to be between 900000 and 1000000, [A: who made this assumption?] yet the observed range is more than tenfold [A: OK].28 In the largest study to date,29 total nephron number ranged from 210332 to 2702079 in 176 adults of African-American ethnic origin and from 227327 to 1660232 in 132 white individuals.

Birthweight correlates linearly with nephron number in adults and children, and nephron number increases by 257426 per kg increase in birthweight,29 suggesting (by extrapolation) that nephron numbers are lower in people with a low birthweight. Although nephron numbers have been measured rarely in adults of known low birthweight, nephron numbers were reduced significantly in infants with low birthweight.30 31 The total number of nephrons in an adult human kidney reflects the number of nephrons formed during development (nephron endowment) minus the number of nephrons subsequently lost; therefore, cumulative injury over time could contribute to a kidney reaching a very low nephron number, leading to disease.32 Human nephrogenesis ends at around 36 weeks of gestation, after which no new nephrons can form.33 In an Australian study, nephron number in 15 infants who died before the age of 3 months ranged 4·5-fold, from 246181 to 1106062, suggesting that much of the variation in nephron number in adults is established before birth.34

Developmental determinants of low nephron number
The most robust clinical surrogates for low nephron number are low birthweight and prematurity. However, not all factors that affect nephron number result in low birthweight, therefore, awareness of risk factors for low nephron number per se is also important (table 1). [A: note that ref 23 is mentioned in the figure legend, I’ve renumbered] The most important risk factors, some of which could be modifiable with public health interventions, include maternal health and nutrition, prenatal and postnatal environments, prematurity, and genetic predisposition.35

Maternal factors
Figure 1 shows maternal health factors that could affect the risk of low birthweight and prematurity and should be judged risk factors for low nephron number in offspring.35 Mothers who themselves were low birthweight, compared with mothers who were not, were more likely to have babies of low birthweight (odds ratio 1·8, 95% CI 1·3–2·5), a finding that is independent of socioeconomic factors, suggesting a genetic or epigenetic intergenerational effect.36

Hypertensive disorders during pregnancy
Disorders linked to high blood pressure in pregnancy were noted in 8·4 million women worldwide in 2004, and these are major risk factors for low birthweight.37 As outlined elsewhere in this series, [A: please provide the reference so we can cross-link papers] risk of pre-eclampsia in a mother is increased if she herself was low birthweight (odds ratio 1·69, 95% CI 1·4–2·02), premature (1·95, 1·54–2·47), or either of the mother’s parents [A: correct?] were born after pre-eclamptic pregnancies (2·2, 2·0–2·4), showing the complexity of intergenerational programming.38 39 Pre-pregnancy maternal chronic kidney disease and hypertension are also relevant risk factors for pre-eclampsia, low birthweight, and preterm delivery.40 In a Cuban cohort,41 maternal hypertension was associated with low birthweight, which in turn was associated with low nephron number.

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Genetics
- RET (14q6.6A) polymorphism: 10% reduction in newborn kidney volume
- PAX2 AAA haplotype: 10% reduction in newborn kidney volume
- Combined RET (14q6.6A) polymorphism and PAX2 AAA haplotype: 23% reduction in newborn kidney volume
- ID ACE polymorphism: 8% reduction in newborn kidney volume
- BMPR1A/22846 polymorphism: 13% reduction in newborn kidney volume
- DSR2/32319305(7) polymorphism: 12% reduction in newborn kidney volume
- Combined DSR1 and RET polymorphisms: 22% reduction in newborn kidney volume
- Combined DSR1 and PAX2 polymorphisms: 27% reduction in newborn kidney volume
- ALDH1A2 (16q289)G polymorphism: 22% increase in newborn kidney size

Adapted from reference 23, with permission of Lippincott Williams and Wilkins. [A: please obtain permission to adapt this table from the publisher] RET = tyrosine kinase receptor. PAX2 = paired box gene 2. ACE = angiotensin-converting enzyme. DSR=Odd-Skipped related. BMPR=bone morphogenetic protein receptor. ALDH=aldehyde dehydrogenase. See appendix for relevant references.

Table 1: Developmental factors associated with nephron number, kidney size, and function

See Online for appendix
Gestational diabetes

The worldwide prevalence of gestational diabetes is poorly recorded, but is reported as 0.1–25.3%. Maternal obesity, now present in 15–20% of pregnancies, is a strong risk factor for gestational diabetes, as is maternal prematurity. In experimental models, maternal hyperglycaemia is associated with reduced nephron number, raised blood pressure, microalbuminuria, and diminished glomerular filtration rate in offspring. In adult children whose mother had diabetes, compared with those who had a diabetic father, renal functional reserve was decreased, suggesting a reduction in nephron number was acquired during exposure to gestational diabetes. Maternal diabetes is also associated with a threefold increased risk of renal agenesis and dysgenesis; therefore, hyperglycaemia strongly affects fetal renal development. Furthermore, gestational diabetes is sometimes associated with high birthweight in infants, which is a known risk factor for subsequent hypertension, type 2 diabetes, renal disease, and cardiovascular disease, although the effect on nephron number is unknown.

Maternal behaviour

Smoking by the mother has been associated with low birthweight and low nephron number. Alcohol consumption is linked to a dose-dependent increased risk of prematurity and fetal growth restriction. In experimental models, gestational alcohol exposure impaired embryonic ureteric bud branching, resulting in low nephron number, and could be a risk in human beings.

Prenatal factors

Maternal diets deficient in protein, total calories, or iron all reduce nephron numbers in experimental models and are most usually associated with low birthweight. In human beings, maternal protein and micronutrient deficiencies are common in developing countries, and maternal malnutrition, underweight, iron deficiency, and anaemia are all recognised risk factors for low birthweight. Vitamin A deficiency is also highly prevalent among pregnant women worldwide. In animals, maternal diets deficient in vitamin A, resulting in amounts similar to those seen in deficient people, induce a dose-dependent reduction in nephron number, whereas vitamin A supplementation augments nephron number. Importantly, vitamin A deficiency alone does not cause low birthweight, suggesting the effect of deficiency could be overlooked if normal birthweight were presumed to exclude an adverse developmental environment. The active metabolite of vitamin A—retinoic acid—regulates transcription of RET, a tyrosine kinase receptor important for kidney development. Plausibly, therefore, vitamin A intake could be a vital determinant of nephron number. Indeed, maternal vitamin A deficiency was associated with significantly smaller newborn adjusted renal volume in Indian babies compared with Canadian infants, probably reflecting lower nephron numbers (table 1).

Prematurity

About 9·6% of liveborn babies are premature (figure 2), and prematurity is associated with raised blood pressure, renal disease, and cardiovascular disease in later life. Nephron number correlates with gestational age; in premature infants, nephrogenesis might continue for a period after birth, although glomeruli are large and abnormal and renal maturation seems accelerated. Consistent with these morphological abnormalities, prematurity is a risk factor for acute kidney injury, which is an independent predictor of mortality and subsequent chronic kidney disease in very low birthweight infants.

Postnatal factors

Human nephrogenesis is complete at term; however, ongoing nephrogenesis has been recorded up to 40 days after birth in infants born before 30 weeks of gestation. Thus, a window of vulnerability exists in preterm infants, during which time kidney development can be affected (table 1). Indeed, extrauterine growth restriction was associated with a significantly lower glomerular filtration rate in very low birthweight children at a mean age of 7–6 years; conversely, the frequency of renal impairment was 33% lower at 6–4 years among very low birthweight children who had gained more weight in neonatal intensive care, showing the importance of early nutrition on kidney development. Nephron number was low in premature infants who developed renal failure before death, although whether renal failure was a cause or outcome of low nephron number is unknown.

Many premature infants receive perinatal drugs such as non-steroidal anti-inflammatory agents, glucocorticoids, and aminoglycosides. Extrapolating from experimental models, these and other drugs can affect nephron number and increase the risk of acute kidney injury in infants. However, follow-up of people whose mother was exposed to betamethasone for 48 h before birth did not show any increase in blood pressure at age 30 years compared with those whose mother had received a placebo. Short-term steroids might, therefore, not affect kidney development, but the effects of such common drugs on human nephrogenesis merit further study.

Genetics

Rare genetic and congenital abnormalities resulting in renal hypoplasia contribute to about half of all cases of childhood end-stage renal disease. Common polymorphisms in several genes known to participate in kidney development correlate with altered gene tran-
scription and newborn kidney size, which is proportional to nephron number (table 1). These studies have been undertaken mainly in white populations [A: we avoid ‘Caucasian’ unless you do mean ‘from the Caucasus’. Is white OK or do you mean white European?], therefore implications for other populations need to be investigated. The molecular mechanisms regulating nephrogenesis are reviewed elsewhere. Individual permutations of these genetic variants could account for the wide variability seen in human nephron numbers, because some mutations reduce and some augment kidney volume. Interactions between genetic polymorphisms and environmental circumstances during kidney development have not been studied. Gene microarray analysis of neonatal kidneys has shown global downregulation of gene expression in experimental models of maternal low protein diet or placental insufficiency. Therefore, altered levels of gene expression resulting from a polymorphism could become even more amplified under conditions of superimposed maternal nutrient deficiency, further decreasing nephron number.

Clinical surrogates for nephron number

At present, all reports of human nephron number have come from kidneys obtained at autopsy. In view of the current reliance on autopsy specimens, surrogate markers for nephron number are important (table 2).

Similar to total nephron number, mean glomerular volume varied up to tenfold in an Australian series of 420 kidneys from people in five ethnic groups. Total nephron number differs inversely with mean glomerular volume. An increase in glomerular volume probably reflects compensatory hypertrophy and hyperfiltration in individual nephrons. Indeed, total filtration surface area is fairly well preserved in kidneys with low nephron number, possibly at the expense of increased glomerular pressure, which can accelerate further nephron loss. Moreover, increased glomerular size is a predictor of poorer renal outcomes in African-American populations, Native Americans (Pima Indians), and Indigenous Australians, and without other causes, should be judged a surrogate for low nephron number. In view of the heterogeneity and hypertrophy occurring in glomeruli, kidney size does not correlate consistently with nephron number in adults, but the relation seems linear in infants younger than 3 months.

Birthweight, prematurity, and blood pressure

Studies of monozygotic twins, in which the twin who weighed the least subsequently had higher blood pressure, suggest that environmental programming could be more crucial than genetic factors. Low birthweight and prematurity have been associated consistently with increased risk of higher blood pressure in later life. In a meta-analysis of 27 studies, a 2·28 mm Hg (95% CI 1·24–3·33) increase in systolic blood pressure was recorded in individuals whose

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<td>Low birthweight</td>
<td>Increase of 257·426 glomeruli per kidney, per kg increase in birthweight</td>
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<td>Prematurity</td>
<td>Decrease in glomerular number, proportional to gestational age, in premature compared with term infants</td>
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<td>Sex</td>
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<td>Age</td>
<td>36/6 fewer glomeruli per kidney per year of age older than 18 years (nephron loss)</td>
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<td>Adult height</td>
<td>28 000 more glomeruli per cm increase in height</td>
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<td>Kidney mass</td>
<td>23·459 more glomeruli per g of kidney tissue (in infants)</td>
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<tr>
<td>Glomerular volume</td>
<td>Inverse correlation between glomerular volume and nephron number</td>
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<tr>
<td>Ethnic origin</td>
<td>Reduced number in Indigenous Australians compared with white and black US population</td>
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Possible correlates

Gestational diabetes exposure Decrease in renal functional reserve in offspring of diabetic mothers versus diabetic fathers

Adapted from reference 23, with permission of Lippincott Williams and Wilkins. [A: please obtain permission to adapt this table from the publisher] See appendix for relevant references.
birthweight was less than 2·5 kg, compared with those heavier than 2·5 kg. Unfortunately, in most studies to date, a distinction has not been made between low birthweight as a result of growth restriction at any gestational age and prematurity with appropriate size for gestational age. Therefore, the potential for unmeasured confounding or effect modification by gestational age, growth restriction, or both must be borne in mind.16

Findings of a systematic review of ten studies showed that, in preterm babies born at a mean gestational age of 30–2 weeks and with a mean birthweight of 1·28 kg, blood pressures in later life were 2·5 mm Hg higher (95% CI 1·7–3·3) than in infants born at term.17 Prematurity has been associated predominantly with high, but still normal, blood pressures, because cohorts studied are still fairly young. Overt hypertension has been recorded in two studies of premature babies: in the first, the children were age 2 years and the prevalence of hypertension (defined as systolic or diastolic blood pressure greater than the 95th percentile) was 30% overall; and in the second, pregnant women were age 25 years and chronic hypertension was present in 1·4% of those born preterm compared with 0·8% born at term (odds ratio 1·7, 95% CI 1·32–2·20).16,39 Researchers have tried to dissect the relative roles of prematurity and growth restriction; some suggest prematurity alone is the predominant risk factor, whereas others judge small for gestational age to be most important when ascertaining risk of raised blood pressure and kidney disease.44 These differences show the complex interplay of intrauterine and extraterine events and timing of insults, which vary considerably in premature infants.33

Because odd ratios for risk of high blood pressure were similar between the meta-analysis of low birthweight1a and the systematic review of prematurity,17 and since prematurity does not account for all babies with low birthweight, both low birthweight and prematurity must be deemed important risk factors for high blood pressure. The association starts in early childhood and becomes augmented in adulthood, at which stage blood pressures typically reach hypertensive ranges,35 suggesting the programming effects are compounded by growth, age, and lifestyle.

Nephron number and blood pressure
In rodents, nephrogenesis continues for up to 7–10 days after birth, providing a window—similar to that seen in premature infants—during which postnatal events can affect nephron number. In rats of low birthweight, rescue of nephron number by optimisation of postnatal nutrition abrogated development of subsequent hypertension; conversely, undernutrition after birth of rat pups of normal birthweight led to lower nephron numbers and higher blood pressure.45,46 These data accord with a role of nephron number in hypertension.

In a German cohort of adults who died in accidents,55 nephron numbers were significantly lower among those with hypertension compared with normotensive controls.52 Low nephron numbers have also been associated with raised blood pressure in Indigenous Australians and white populations from the USA and Australia, although birthweights were unknown.44 The relation between nephron number and blood pressure in people of African origin seems less clear, but glomerular volume is a significant independent predictor of high blood pressure in this population.44 Additional factors probably contribute to hypertension in African populations, but the effect of birthweight or the contribution of nephron number to severity of hypertension, for example, cannot be excluded.

Observations in patients [A: ref?] of normalisation of glomerular filtration surface area despite low nephron numbers argue against the hypothesis that sodium excretion is restricted. However, in patients and in experimental models, low birthweight and low nephron number were associated with a salt-induced increase in blood pressure (panel).65,66 Salt sensitivity in young adults and children correlates inversely with birthweight, independent of glomerular filtration rate, suggesting a primary defect in renal sodium handling.47,48

Evidence that hypertension is not eliminated despite normalisation of nephron number in some experimental models suggests that additional factors participate in developmental programming of hypertension.49 Experimental work has shown alterations in renal tubule sodium transporter expression and systemic changes in vascular function, neuroendocrine adaptations to stress, insulin sensitivity, and sympathetic nervous system activity.50 Nephron number, therefore, is not the sole programmed risk factor for hypertension, but it is likely to exacerbate any risk and contribute to kidney disease.

**Renal function, birthweight, and nephron mass**

**Glomerular filtration rate**
Without compensatory hyperfiltration, a kidney with a reduced number of nephrons should have a diminished glomerular filtration rate. Indeed, glomerular filtration rate extrapolated from amikacin clearance on day 1 of life, preceding any compensatory adaptation, was decreased significantly in premature and low-birthweight infants compared with term controls.51 Glomerular filtration rate measured by inulin clearance was significantly lower at age 7–6 years in children who had been born premature and had severe growth restriction compared with non-growth-restricted controls.52 In this study, the effects were similar in children who were growth-restricted prenatally or postnatally in intensive care, again showing the importance of early nutrition. In a meta-analysis of eight studies,63 the odds ratio for reduced glomerular filtration rate with low birthweight was 1·79 (95% CI 1·31–2·45).

**Proteinuria**
Microalbuminuria is one of the earliest signs of glomerular hyperfiltration, and transition to macroalbuminuria accords with ongoing renal injury. Hoy and
Programming includes quite variable and needs further elaboration in a meta-analysis of nine studies. The odds ratio of 1.81 (95% CI 1.19–2.77) for albuminuria in low-birthweight individuals has been confirmed in many studies. Chronic kidney disease and end-stage renal disease Amplified progression of primary renal diseases has been noted in low-birthweight. A study of 22-year-old British adults showed that the odds ratio for chronic kidney disease (including end-stage renal disease) associated with low birthweight was 1.73 (95% CI 1.44–2.08) from 18 studies. In population-based studies, a U-shaped relation has been reported between birthweight and risk of chronic kidney disease or end-stage renal disease, suggesting high birthweight is also important. In some studies, the programmed risk of chronic kidney disease seems to be greater in men. However, the differential effect of sex on renal programming is quite variable and needs further study.

Similar to programming of blood pressure risk, the number of nephrons is unlikely to be the sole factor contributing to renal disease, and a low nephron number will probably not be sufficient to cause renal disease without additional variables. Moreover, developmental programming of disorders—e.g., type 2 diabetes, cardiovascular disease, insulin resistance, and obesity—could increase renal risk further. Programming of these disorders might take place simultaneously in a developing fetus, depending on timing and nature of the insults. All infants subjected to adverse intrauterine conditions should be judged at risk for all these disorders.

Effect of childhood weight gain on kidney disease and function Postnatal malnourishment and clinical circumstances can affect nephrogenesis, childhood renal function, and long-term risk of renal disease (figure 1). In rats with low birthweight, low nephron numbers were restored to normal and development of hypertension was abrogated by provision of adequate postnatal nutrition. When low-birthweight rats were overfed after birth, nephron numbers remained low and the rodents developed obesity, hypertension, and renal injury over time. In rats with normal birthweight that were overfed postnatally, despite a higher-than-normal nephron number, blood pressure, proteinuria, and glomerulosclerosis were all increased in adulthood. Taken together, these data suggest that normalisation of postnatal nutrition can be beneficial, but overfeeding is probably deleterious. In infants, postnatal weight gain and nutrition have been implicated in developmental programming of adult disease.

Catch-up growth in children who were of low birthweight has long been advocated, particularly in developing countries, to boost resilience against infections and reduce risk of undernutrition, stunting, and cognitive impairment. However, in many populations worldwide, accelerated weight gain or an increase in body-mass index, even in children with a normal birthweight, has been associated consistently with amplified risk of adult hypertension, type 2 diabetes, and cardiovascular disease. This effect grows as the child ages: upward crossing of weight or body-mass index percentiles in mid-childhood or adolescence is associated with strong adverse effects on later risk, whereas upward crossing in infancy (younger than 1 year) has no or little effect on later blood pressure and could protect against diabetes. The gain in body-mass index associated with increased risk of adult disease is not always excessive in terms of absolute number. In many developing countries, children who gain rapidly can still be small by international weight standards, but upwards crossing of body-mass index percentiles seems to be the important factor. Therefore, one cross-sectional measurement of a child’s weight or body-mass index could be misleading in such circumstances, emphasising the need for growth tracking in early childhood.

Children born with a low birthweight who have an adequate nutrient supply tend to gain weight rapidly. Among 22-year-old British adults, systolic blood pressure increased by 1.3 mm Hg (95% CI 0.3–2.3) for every SD decrease in birthweight and rose by 1.6 mm Hg (0.6–2.7) for every SD gain in childhood weight between age 1 year and 10 years. An association is well recognised between rapid childhood weight gain and raised blood pressure and increased arterial stiffness, which is sometimes already evident in childhood.

In a study of 2,167,711 Scandinavian adults, those with a birthweight of 2.5 kg and a body-mass index of 17.7 kg/m² (overweight) at age 7 years had a 44% increased risk of cardiovascular disease in adulthood compared with those with a median birthweight of 3.4 kg and a body-mass index of 15.3 kg/m² at age 7 years. The highest risk of raised blood pressure and cardiovascular disease,
therefore, was present in children born with low birthweight who became heavy. Importantly, body-mass index was associated strongly and positively with cardiovascular disease risk in this study, independent of birthweight, showing the importance of childhood obesity itself as a risk factor for adult disease.

The prevalence of childhood obesity is increasing worldwide (figure 2). Risk factors for obesity include high birthweight, exposure to gestational diabetes, and early postnatal weight gain. These factors are also associated independently with altered nephrogenesis and increased risk of hypertension, type 2 diabetes, and renal dysfunction (figure 1). Furthermore, obesity per se is a risk factor for progression of renal disease; therefore, superimposition of the burden of obesity on a small kidney with fewer nephrons is likely to compound the risk and act as a second hit, accelerating renal disease progression. How can we optimise postnatal growth and positively change any subsequent disease risk, particularly in low-birthweight infants? Avoidance of obesity seems to be a safe guiding principle.

Early growth and kidney function
The association of rapid childhood weight gain with high blood pressure, diabetes, and obesity is likely to compound any primary programmed renal risk. Indeed, in a retrospective analysis of 80 children with proteimuric kidney disease, renal disease progressed fastest in those who had been premature and became obese. Glomerular size was increased in all obese children, whether premature or term, whereas kidney size remained small in all those who had been premature, independent of obesity. Similarly, among infants with very low birthweight who developed neonatal acute kidney injury, excessive weight gain was a predictor of poorer renal function at a mean age of 7-5 (SD 4-6) years. The effect of infant weight gain on long-term renal function remains unknown.

Mechanisms linking kidney disease and weight gain
Several mechanisms have been proposed to explain the amplification of renal and cardiovascular disease risk by rapid weight gain after growth restriction. One possibility is development of premature senescence. Cellular senescence is a state of growth arrest induced by upregulation of the cell-cycle inhibitors P53, P21, and PI6INK4a. Upregulation of the genes for these proteins can be induced by progressive telomere shortening, which takes place with cell replication and is a robust marker of ageing, and by reactive oxygen species induced by cellular stress.

Chronic cardiovascular and renal diseases are associated with increased expression of senescence markers. In experimental models, low birthweight followed by rapid postnatal weight gain was associated with shorter telomeres and amplified expression of senescence markers in the kidneys, heart, and aorta, in addition to premature death, which all accord with accelerated ageing. Low birthweight was also associated with higher renal and cardiovascular mortality in an Indigenous Australian cohort, which accords with these experimental findings.

Premature senescence in the kidney might be attributable to ongoing hyperfiltration injury in kidneys with a few nephrons, compounded by a rapid increase in body size. Leukocyte telomere length did not differ between British babies of low and normal birthweight, but among 5-year-old children from Bangladesh, telomeres were significantly shorter in those who were of low birthweight.

Senescence is linked to oxidative stress. In children born small for gestational age, compared with controls [A: how were controls matched? Appropriate size for gestational age?], markers of oxidative stress were highest in those who experienced catch-up growth. The link between nephron numbers, catch-up growth, premature senescence, and development of hypertension and renal disease seems plausible, but it has not yet been confirmed.

Conclusion
The association between fetal and childhood development and increased risk of adult disease is now quite convincing. Low birthweight and prematurity are associated with raised blood pressure and decreased renal function, manifesting in early childhood, which could progress to overt disease in adulthood. Nutrition is a cornerstone of this association. Maternal nutrition and health before and during pregnancy are crucial for fetal growth and for development of a kidney with enough nephrons to maintain homeostasis in response to dietary and metabolic stresses and to sustain function in the face of superimposed nephron loss. Early postnatal nutrition, particularly after premature birth, is also important for renal development. Furthermore, upward crossing of weight or body-mass index percentiles after the infant period programmes risk of hypertension and renal disease. Developmental programming has an intergenerational effect, because low birthweight increases the risk of maternal pre-eclampsia, obesity, and gestational diabetes, which all in turn further compound future risks in their offspring.

Growing knowledge and understanding of the pathophysiology of developmental programming has identified at-risk populations that could be targets for screening and interventions to interrupt this cycle. Identification of nutritional deficiencies within populations (eg, vitamin A deficiency) ought to prompt public health interventions to correct these deficiencies well before pregnancy. Adequate antenatal care should identify women who develop pre-eclampsia and gestational diabetes, optimise their care during pregnancy, but lead to lifestyle education and lifelong screening of these women for later disease. Currently, a few women worldwide are screened for gestational diabetes. With the rising prevalence of...
In later life, regular cardiovascular exercise abrogates the metabolic outcomes of being small at birth among men. Identification of at-risk pregnancies and offspring of both high and low birthweight should prompt maternal education to optimise childhood nutrition and activity to prevent obesity. Prematurity and low birthweight are among the top ten contributors to the global burden of disease, calculations that might not always have included the long-term costs of programmed adult non-communicable diseases. Acknowledgment of the role of developmental programming in hypertension and renal disease risk, and implementation of locally adapted preventive strategies in individual countries, will have important long-term benefits in terms of future health, productivity, and cost savings worldwide.

Contributors

[A: please provide a signed statement from every author, stating their contribution to the paper]

Conflicts of interest

We declare that we have no conflicts of interest.

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